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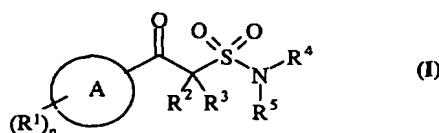
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(54) Title: 2-OXO-ETHANESULFONAMIDE DERIVATES



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(57) Abstract: Compounds of formula (I): Formula (I) wherein variable groups are as defined within; for use in the inhibition of 11 $\beta$ HSD1 are described.

## 2-OXO-ETHANESULFONAMIDE DERIVATES

This invention relates to chemical compounds, or pharmaceutically acceptable salts thereof. These compounds possess human 11- $\beta$ -hydroxysteroid dehydrogenase type 1 enzyme (11 $\beta$ HSD1) inhibitory activity and accordingly have value in the treatment of disease states including metabolic syndrome and are useful in methods of treatment of a warm-blooded animal, such as man. The invention also relates to processes for the manufacture of said compounds, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments to inhibit 11 $\beta$ HSD1 in a warm-blooded animal, such as man.

Glucocorticoids (cortisol in man, corticosterone in rodents) are counter regulatory hormones i.e. they oppose the actions of insulin (Dallman MF, Strack AM, Akana SF et al. 1993; Front Neuroendocrinol 14, 303-347). They regulate the expression of hepatic enzymes involved in gluconeogenesis and increase substrate supply by releasing glycerol from adipose tissue (increased lipolysis) and amino acids from muscle (decreased protein synthesis and increased protein degradation). Glucocorticoids are also important in the differentiation of pre-adipocytes into mature adipocytes which are able to store triglycerides (Bujalska IJ et al. 1999; Endocrinology 140, 3188-3196). This may be critical in disease states where glucocorticoids induced by "stress" are associated with central obesity which itself is a strong risk factor for type 2 diabetes, hypertension and cardiovascular disease (Bjorntorp P & Rosmond R 2000; Int. J. Obesity 24, S80-S85)

It is now well established that glucocorticoid activity is controlled not simply by secretion of cortisol but also at the tissue level by intracellular interconversion of active cortisol and inactive cortisone by the 11-beta hydroxysteroid dehydrogenases, 11 $\beta$ HSD1 (which activates cortisone) and 11 $\beta$ HSD2 (which inactivates cortisol) (Sandeep TC & Walker BR 2001 Trends in Endocrinol & Metab. 12, 446-453). That this mechanism may be important in man was initially shown using carbenoxolone (an anti-ulcer drug which inhibits both 11 $\beta$ HSD1 and 2) treatment which (Walker BR et al. 1995; J. Clin. Endocrinol. Metab. 80, 3155-3159) leads to increased insulin sensitivity indicating that 11 $\beta$ HSD1 may well be regulating the effects of insulin by decreasing tissue levels of active glucocorticoids (Walker BR et al. 1995; J. Clin. Endocrinol. Metab. 80, 3155-3159).

Clinically, Cushing's syndrome is associated with cortisol excess which in turn is associated with glucose intolerance, central obesity (caused by stimulation of pre-adipocyte differentiation in this depot), dyslipidaemia and hypertension. Cushing's syndrome shows a

number of clear parallels with metabolic syndrome. Even though the metabolic syndrome is not generally associated with excess circulating cortisol levels (Jessop DS et al. 2001; J. Clin. Endocrinol. Metab. 86, 4109-4114) abnormally high 11 $\beta$ HSD1 activity within tissues would be expected to have the same effect. In obese men it was shown that despite having similar or 5 lower plasma cortisol levels than lean controls, 11 $\beta$ HSD1 activity in subcutaneous fat was greatly enhanced (Rask E et al. 2001; J. Clin. Endocrinol. Metab. 1418-1421). Furthermore, the central fat, associated with the metabolic syndrome expresses much higher levels of 11 $\beta$ HSD1 activity than subcutaneous fat (Bujalska IJ et al. 1997; Lancet 349, 1210-1213). Thus there appears to be a link between glucocorticoids, 11 $\beta$ HSD1 and the metabolic 10 syndrome.

11 $\beta$ HSD1 knock-out mice show attenuated glucocorticoid-induced activation of gluconeogenic enzymes in response to fasting and lower plasma glucose levels in response to stress or obesity (Kotelevtsev Y et al. 1997; Proc. Natl. Acad. Sci USA 94, 14924-14929) indicating the utility of inhibition of 11 $\beta$ HSD1 in lowering of plasma glucose and hepatic 15 glucose output in type 2 diabetes. Furthermore, these mice express an anti-atherogenic lipoprotein profile, having low triglycerides, increased HDL cholesterol and increased apo-lipoprotein AI levels. (Morton NM et al. 2001; J. Biol. Chem. 276, 41293-41300). This phenotype is due to an increased hepatic expression of enzymes of fat catabolism and PPAR $\alpha$ . Again this indicates the utility of 11 $\beta$ HSD1 inhibition in treatment of the 20 dyslipidaemia of the metabolic syndrome.

The most convincing demonstration of a link between the metabolic syndrome and 11 $\beta$ HSD1 comes from recent studies of transgenic mice over-expressing 11 $\beta$ HSD1 (Masuzaki H et al. 2001; Science 294, 2166-2170). When expressed under the control of an adipose specific promoter, 11 $\beta$ HSD1 transgenic mice have high adipose levels of 25 corticosterone, central obesity, insulin resistant diabetes, hyperlipidaemia and hyperphagia. Most importantly, the increased levels of 11 $\beta$ HSD1 activity in the fat of these mice are similar to those seen in obese subjects. Hepatic 11 $\beta$ HSD1 activity and plasma corticosterone levels were normal, however, hepatic portal vein levels of corticosterone were increased 3 fold and it is thought that this is the cause of the metabolic effects in liver.

30 Overall it is now clear that the complete metabolic syndrome can be mimicked in mice simply by overexpressing 11 $\beta$ HSD1 in fat alone at levels similar to those in obese man.

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11 $\beta$ HSD1 tissue distribution is widespread and overlapping with that of the glucocorticoid receptor. Thus, 11 $\beta$ HSD1 inhibition could potentially oppose the effects of glucocorticoids in a number of physiological/pathological roles. 11 $\beta$ HSD1 is present in human skeletal muscle and glucocorticoid opposition to the anabolic effects of insulin on protein turnover and glucose metabolism are well documented (Whorwood CB et al. 2001; J. Clin. Endocrinol. Metab. 86, 2296-2308). Skeletal muscle must therefore be an important target for 11 $\beta$ HSD1 based therapy.

Glucocorticoids also decrease insulin secretion and this could exacerbate the effects of glucocorticoid induced insulin resistance. Pancreatic islets express 11 $\beta$ HSD1 and carbenoxolone can inhibit the effects of 11-dehydrocorticosterone on insulin release (Davani B et al. 2000; J. Biol. Chem. 275, 34841-34844). Thus in treatment of diabetes 11 $\beta$ HSD1 inhibitors may not only act at the tissue level on insulin resistance but also increase insulin secretion itself.

Skeletal development and bone function is also regulated by glucocorticoid action. 11 $\beta$ HSD1 is present in human bone osteoclasts and osteoblasts and treatment of healthy volunteers with carbenoxolone showed a decrease in bone resorption markers with no change in bone formation markers (Cooper MS et al 2000; Bone 27, 375-381). Inhibition of 11 $\beta$ HSD1 activity in bone could be used as a protective mechanism in treatment of osteoporosis.

Glucocorticoids may also be involved in diseases of the eye such as glaucoma. 11 $\beta$ HSD1 has been shown to affect intraocular pressure in man and inhibition of 11 $\beta$ HSD1 may be expected to alleviate the increased intraocular pressure associated with glaucoma (Rauz S et al. 2001; Investigative Ophthalmology & Visual Science 42, 2037-2042).

There appears to be a convincing link between 11 $\beta$ HSD1 and the metabolic syndrome both in rodents and in humans. Evidence suggests that a drug which specifically inhibits 11 $\beta$ HSD1 in type 2 obese diabetic patients will lower blood glucose by reducing hepatic gluconeogenesis, reduce central obesity, improve the atherogenic lipoprotein phenotype, lower blood pressure and reduce insulin resistance. Insulin effects in muscle will be enhanced and insulin secretion from the beta cells of the islet may also be increased.

Currently there are two main recognised definitions of metabolic syndrome.

- 1) The Adult Treatment Panel (ATP III 2001 JMA) definition of metabolic syndrome indicates that it is present if the patient has three or more of the following symptoms:

- 4 -

- Waist measuring at least 40 inches (102 cm) for men, 35 inches (88 cm) for women;
- Serum triglyceride levels of at least 150 mg/dl (1.69 mmol/l);
- HDL cholesterol levels of less than 40 mg/dl (1.04 mmol/l) in men, less than 50 mg/dl (1.29 mmol/l) in women;

5      ➤ Blood pressure of at least 135/80 mm Hg; and / or

- Blood sugar (serum glucose) of at least 110 mg/dl (6.1 mmol/l).

2) The WHO consultation has recommended the following definition which does not imply causal relationships and is suggested as a working definition to be improved upon in due course:

10     ➤ The patient has at least one of the following conditions: glucose intolerance, impaired glucose tolerance (IGT) or diabetes mellitus and/or insulin resistance; together with two or more of the following:

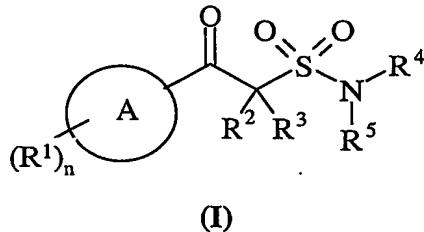
- Raised Arterial Pressure;
- Raised plasma triglycerides

15     ➤ Central Obesity

- Microalbuminuria

We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective 11 $\beta$ HSD1inhibitors, and accordingly have value in the treatment of disease states associated with metabolic syndrome.

20     Accordingly there is provided the use of a compound of formula (I):



wherein:

**Ring A** is selected from carbocyclyl or heterocyclyl;

25     **R<sup>1</sup>** is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, N-(C<sub>1-4</sub>alkyl)amino, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, C<sub>1-4</sub>alkanoylamino, N-(C<sub>1-4</sub>alkyl)carbamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, N-(C<sub>1-4</sub>alkyl)sulphamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino, 30 tri-(C<sub>1-4</sub>alkyl)silyloxy, carbocyclyl, heterocyclyl, carbocyclylC<sub>0-4</sub>alkylene-Y- and

- 5 -

heterocycllC<sub>0-4</sub>alkylene-Y-; wherein R<sup>1</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>; and wherein if said heterocycll contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R<sup>7</sup>;

n is 0-5; wherein the values of R<sup>1</sup> may be the same or different;

5 R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen, hydroxy, amino, cyano, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, N-(C<sub>1-4</sub>alkyl)amino, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, carbocycll, heterocycll, carbocycllC<sub>1-4</sub>alkyl, heterocycllC<sub>1-4</sub>alkyl; or R<sup>2</sup> and R<sup>3</sup> together form C<sub>2-6</sub>alkylene; wherein R<sup>2</sup> and R<sup>3</sup> may be independently optionally substituted on carbon by one or more groups selected from R<sup>8</sup>; and wherein if said heterocycll contains an -NH- moiety that nitrogen may 10 be optionally substituted by a group selected from R<sup>9</sup>;

one of R<sup>4</sup> and R<sup>5</sup> is selected from C<sub>1-4</sub>alkyl and the other is selected from hydrogen or C<sub>1-4</sub>alkyl; wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>;

Y is -S(O)<sub>a</sub>-, -O-, -NR<sup>12</sup>-, -C(O), -C(O)NR<sup>13</sup>-, -NR<sup>14</sup>C(O)- or -SO<sub>2</sub>NR<sup>15</sup>-; wherein a is 15 0 to 2;

R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup> and R<sup>15</sup> are independently selected from hydrogen, phenyl and C<sub>1-4</sub>alkyl;

R<sup>6</sup> and R<sup>8</sup> are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, N-(C<sub>1-4</sub>alkyl)amino, 20 N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, C<sub>1-4</sub>alkanoylamino, N-(C<sub>1-4</sub>alkyl)carbamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, N-(C<sub>1-4</sub>alkyl)sulphamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino, carbocycll and heterocycll; wherein R<sup>6</sup> and R<sup>8</sup> may be independently optionally substituted on carbon by one or more R<sup>11</sup>;

25 R<sup>10</sup> is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, N-(C<sub>1-4</sub>alkyl)amino, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, C<sub>1-4</sub>alkanoylamino, N-(C<sub>1-4</sub>alkyl)carbamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, N-(C<sub>1-4</sub>alkyl)sulphamoyl,

30 N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino; wherein R<sup>10</sup> may be independently optionally substituted on carbon by one or more R<sup>16</sup>;

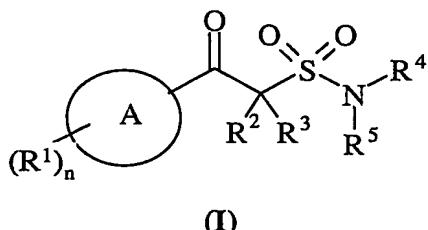
**R<sup>7</sup>** and **R<sup>9</sup>** are independently selected from C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkylsulphonyl, C<sub>1-4</sub>alkoxycarbonyl, carbamoyl, N-(C<sub>1-4</sub>alkyl)carbamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

**R<sup>11</sup>** and **R<sup>16</sup>** are independently selected from halo, nitro, cyano, hydroxy,

- 5 trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylarnino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulphanyl, ethylsulphanyl, mesyl, ethylsulphonyl, methoxycarbonyl,
- 10 ethoxycarbonyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl or N-methyl-N-ethylsulphamoyl;
- or a pharmaceutically acceptable salt thereof;
- in the manufacture of a medicament for use in the inhibition of 11 $\beta$ HSD1.

According to a further feature of the invention there is provided the use of a compound

- 15 of formula (I):



wherein:

**Ring A** is selected from aryl or heteroaryl;

- 20 **R<sup>1</sup>** is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, N-(C<sub>1-4</sub>alkyl)amino, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, C<sub>1-4</sub>alkanoylamino, N-(C<sub>1-4</sub>alkyl)carbamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, N-(C<sub>1-4</sub>alkyl)sulphamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino, carbocyclyl, heterocyclyl, carbocyclylC<sub>0-4</sub>alkylene-Y- and heterocyclylC<sub>0-4</sub>alkylene-Y-; or two R<sup>1</sup> on adjacent carbons may form an oxyC<sub>1-4</sub>alkoxy group; wherein R<sup>1</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R<sup>7</sup>;
- 25 **n** is 0-3; wherein the values of R<sup>1</sup> may be the same or different;

**R<sup>2</sup>** and **R<sup>3</sup>** are independently selected from hydrogen, hydroxy, amino, cyano, C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, N-(C<sub>1-4</sub>alkyl)amino, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, carbocyclyl, heterocyclyl, carbocyclylC<sub>1-4</sub>alkyl, heterocyclylC<sub>1-4</sub>alkyl; wherein R<sup>2</sup> and R<sup>3</sup> may be independently optionally substituted on carbon by one or more groups selected from R<sup>8</sup>; and wherein if said

5 heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R<sup>9</sup>;

**R<sup>4</sup>** and **R<sup>5</sup>** are independently selected from C<sub>1-4</sub>alkyl; wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>;

Y is -S(O)<sub>a</sub>- , -O-, -NR<sup>12</sup>- , -C(O), -C(O)NR<sup>13</sup>- , -NR<sup>14</sup>C(O)- or -SO<sub>2</sub>NR<sup>15</sup>- ; wherein a is

10 0 to 2;

**R<sup>12</sup>**, **R<sup>13</sup>**, **R<sup>14</sup>** and **R<sup>15</sup>** are independently selected from hydrogen, phenyl and C<sub>1-4</sub>alkyl;

**R<sup>6</sup>** and **R<sup>8</sup>** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, N-(C<sub>1-4</sub>alkyl)amino,

15 **N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino**, C<sub>1-4</sub>alkanoylamino, **N-(C<sub>1-4</sub>alkyl)carbamoyl**,

**N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl**, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, **N-(C<sub>1-4</sub>alkyl)sulphamoyl**, **N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl**, C<sub>1-4</sub>alkylsulphonylamino, carbocyclyl and heterocyclyl; wherein R<sup>6</sup> and R<sup>8</sup> may be independently optionally substituted on carbon by one or more R<sup>11</sup>;

20 **R<sup>10</sup>** is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, N-(C<sub>1-4</sub>alkyl)amino, **N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino**, **C<sub>1-4</sub>alkanoylamino**, **N-(C<sub>1-4</sub>alkyl)carbamoyl**, **N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl**, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, **N-(C<sub>1-4</sub>alkyl)sulphamoyl**,

25 **N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl**, C<sub>1-4</sub>alkylsulphonylamino; wherein R<sup>10</sup> may be independently optionally substituted on carbon by one or more R<sup>16</sup>;

**R<sup>7</sup>** and **R<sup>9</sup>** are independently selected from C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkylsulphonyl, C<sub>1-4</sub>alkoxycarbonyl, carbamoyl, N-(C<sub>1-4</sub>alkyl)carbamoyl, **N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl**, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

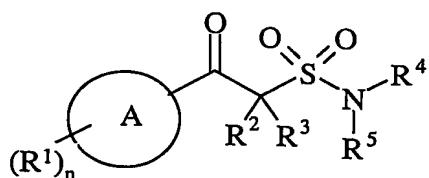
30 **R<sup>11</sup>** and **R<sup>16</sup>** are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, **N-methyl-N-ethylamino**, **acetylamino**, **N-methylcarbamoyl**, **N-ethylcarbamoyl**,

*N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;

5 or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11 $\beta$ HSD1.

According to a further feature of the invention there is provided the use of a compound of formula (I):



10

(I)

wherein:

**Ring A** is selected from carbocyclyl or heterocyclyl;

**R¹** is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy,

15 *N*-(C<sub>1-4</sub>alkyl)amino, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, C<sub>1-4</sub>alkanoylamino, *N*-(C<sub>1-4</sub>alkyl)carbamoyl, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, *N*-(C<sub>1-4</sub>alkyl)sulphamoyl, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino, tri-(C<sub>1-4</sub>alkyl)silyloxy, carbocyclyl, heterocyclyl, carbocyclylC<sub>0-4</sub>alkylene-Y- and heterocyclylC<sub>0-4</sub>alkylene-Y-; wherein R<sup>1</sup> may be optionally substituted on carbon by one or

20 more groups selected from R<sup>6</sup>; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R<sup>7</sup>;

**n** is 0-3; wherein the values of R<sup>1</sup> may be the same or different;

**R<sup>2</sup>** and **R<sup>3</sup>** are independently selected from hydrogen, hydroxy, amino, cyano,

C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, *N*-(C<sub>1-4</sub>alkyl)amino, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, carbocyclyl, heterocyclyl,

25 carbocyclylC<sub>1-4</sub>alkyl, heterocyclylC<sub>1-4</sub>alkyl; wherein R<sup>2</sup> and R<sup>3</sup> may be independently optionally substituted on carbon by one or more groups selected from R<sup>8</sup>; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R<sup>9</sup>;

one of  $\mathbf{R}^4$  and  $\mathbf{R}^5$  is selected from  $C_{1-4}$ alkyl and the other is selected from hydrogen or  $C_{1-4}$ alkyl; wherein  $\mathbf{R}^4$  and  $\mathbf{R}^5$  may be optionally substituted on carbon by one or more groups selected from  $\mathbf{R}^{10}$ ;

$\mathbf{Y}$  is  $-S(O)_a-$ ,  $-O-$ ,  $-NR^{12}-$ ,  $-C(O)$ ,  $-C(O)NR^{13}-$ ,  $-NR^{14}C(O)-$  or  $-SO_2NR^{15}-$ ; wherein  $a$  is

5 0 to 2;

$\mathbf{R}^{12}$ ,  $\mathbf{R}^{13}$ ,  $\mathbf{R}^{14}$  and  $\mathbf{R}^{15}$  are independently selected from hydrogen, phenyl and  $C_{1-4}$ alkyl;

$\mathbf{R}^6$  and  $\mathbf{R}^8$  are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy,  $C_{1-4}$ alkyl,  $C_{2-4}$ alkenyl,  $C_{2-4}$ alkynyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkanoyl,  $C_{1-4}$ alkanoyloxy,  $N-(C_{1-4}$ alkyl)amino,

10  $N,N-(C_{1-4}$ alkyl)<sub>2</sub>amino,  $C_{1-4}$ alkanoylamino,  $N-(C_{1-4}$ alkyl)carbamoyl,

$N,N-(C_{1-4}$ alkyl)<sub>2</sub>carbamoyl,  $C_{1-4}$ alkylS(O)<sub>a</sub> wherein  $a$  is 0 to 2,  $C_{1-4}$ alkoxycarbonyl,

$N-(C_{1-4}$ alkyl)sulphamoyl,  $N,N-(C_{1-4}$ alkyl)<sub>2</sub>sulphamoyl,  $C_{1-4}$ alkylsulphonylamino, carbocyclyl and heterocyclyl; wherein  $\mathbf{R}^6$  and  $\mathbf{R}^8$  may be independently optionally substituted on carbon by one or more  $\mathbf{R}^{11}$ ;

15  $\mathbf{R}^{10}$  is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy,  $C_{1-4}$ alkyl,  $C_{2-4}$ alkenyl,  $C_{2-4}$ alkynyl,  $C_{1-4}$ alkoxy,  $C_{1-4}$ alkanoyl,  $C_{1-4}$ alkanoyloxy,  $N-(C_{1-4}$ alkyl)amino,  $N,N-(C_{1-4}$ alkyl)<sub>2</sub>amino,  $C_{1-4}$ alkanoylamino,  $N-(C_{1-4}$ alkyl)carbamoyl,  $N,N-(C_{1-4}$ alkyl)<sub>2</sub>carbamoyl,  $C_{1-4}$ alkylS(O)<sub>a</sub> wherein  $a$  is 0 to 2,  $C_{1-4}$ alkoxycarbonyl,  $N-(C_{1-4}$ alkyl)sulphamoyl,

20  $N,N-(C_{1-4}$ alkyl)<sub>2</sub>sulphamoyl,  $C_{1-4}$ alkylsulphonylamino; wherein  $\mathbf{R}^{10}$  may be independently optionally substituted on carbon by one or more  $\mathbf{R}^{16}$ ;

$\mathbf{R}^7$  and  $\mathbf{R}^9$  are independently selected from  $C_{1-4}$ alkyl,  $C_{1-4}$ alkanoyl,  $C_{1-4}$ alkylsulphonyl,  $C_{1-4}$ alkoxycarbonyl, carbamoyl,  $N-(C_{1-4}$ alkyl)carbamoyl,  $N,N-(C_{1-4}$ alkyl)<sub>2</sub>carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

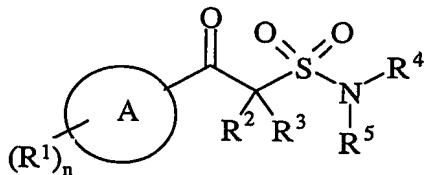
25  $\mathbf{R}^{11}$  and  $\mathbf{R}^{16}$  are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino,  $N$ -methyl- $N$ -ethylamino, acetylamino,  $N$ -methylcarbamoyl,  $N$ -ethylcarbamoyl,  $N,N$ -dimethylcarbamoyl,  $N,N$ -diethylcarbamoyl,  $N$ -methyl- $N$ -ethylcarbamoyl, methylthio,

30 ethylthio, methylsulphanyl, ethylsulphanyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl,  $N$ -methylsulphamoyl,  $N$ -ethylsulphamoyl,  $N,N$ -dimethylsulphamoyl,  $N,N$ -diethylsulphamoyl or  $N$ -methyl- $N$ -ethylsulphamoyl;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of  $11\beta$ HSD1.

According to a further feature of the invention there is provided a compound of formula (Ia):



5

(Ia)

wherein:

**Ring A** is selected from phenyl, pyridyl, thiazolyl, thienyl and furyl;

**R¹** is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>2</sub>-C<sub>4</sub>alkenyl, C<sub>2</sub>-C<sub>4</sub>alkynyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkanoyl, C<sub>1</sub>-C<sub>4</sub>alkanoyloxy,

10 **N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)amino, **N,N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>amino, C<sub>1</sub>-C<sub>4</sub>alkanoylamino, **N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)carbamoyl, **N,N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1</sub>-C<sub>4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1</sub>-C<sub>4</sub>alkoxycarbonyl, **N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)sulphamoyl, **N,N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1</sub>-C<sub>4</sub>alkylsulphonylamino; wherein R<sup>1</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a 15 group selected from R<sup>7</sup>;

**n** is 0-3; wherein the values of R<sup>1</sup> may be the same or different;

**R<sup>2</sup>** and **R<sup>3</sup>** are independently selected from hydrogen, hydroxy, amino, cyano, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, **N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)amino, **N,N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>amino, carbocyclyl, heterocyclyl, carbocyclylC<sub>1</sub>-C<sub>4</sub>alkyl, heterocyclylC<sub>1</sub>-C<sub>4</sub>alkyl; wherein R<sup>2</sup> and R<sup>3</sup> may be independently

20 optionally substituted on carbon by one or more groups selected from R<sup>8</sup>; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R<sup>9</sup>;

**R<sup>4</sup>** and **R<sup>5</sup>** are independently selected from C<sub>1</sub>-C<sub>4</sub>alkyl; wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>;

25 **R<sup>6</sup>** and **R<sup>8</sup>** are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C<sub>1</sub>-C<sub>4</sub>alkyl, C<sub>2</sub>-C<sub>4</sub>alkenyl, C<sub>2</sub>-C<sub>4</sub>alkynyl, C<sub>1</sub>-C<sub>4</sub>alkoxy, C<sub>1</sub>-C<sub>4</sub>alkanoyl, C<sub>1</sub>-C<sub>4</sub>alkanoyloxy, **N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)amino, **N,N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>amino, C<sub>1</sub>-C<sub>4</sub>alkanoylamino, **N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)carbamoyl, **N,N**-(C<sub>1</sub>-C<sub>4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1</sub>-C<sub>4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1</sub>-C<sub>4</sub>alkoxycarbonyl,

*N*-(C<sub>1-4</sub>alkyl)sulphamoyl, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino; wherein R<sup>6</sup> and R<sup>8</sup> may be independently optionally substituted on carbon by one or more R<sup>11</sup>;

R<sup>10</sup> is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl,  
5 C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, *N*-(C<sub>1-4</sub>alkyl)amino, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, C<sub>1-4</sub>alkanoylamino, *N*-(C<sub>1-4</sub>alkyl)carbamoyl, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, *N*-(C<sub>1-4</sub>alkyl)sulphamoyl, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino; wherein R<sup>10</sup> may be independently optionally substituted on carbon by one or more R<sup>16</sup>;

10 R<sup>7</sup> and R<sup>9</sup> are independently selected from C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkylsulphonyl, C<sub>1-4</sub>alkoxycarbonyl, carbamoyl, *N*-(C<sub>1-4</sub>alkyl)carbamoyl, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R<sup>11</sup> and R<sup>16</sup> are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl,  
15 methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, *N*-methyl-*N*-ethylamino, acetylamino, *N*-methylcarbamoyl, *N*-ethylcarbamoyl, *N,N*-dimethylcarbamoyl, *N,N*-diethylcarbamoyl, *N*-methyl-*N*-ethylcarbamoyl, methylthio, ethylthio, methylsulphanyl, ethylsulphanyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl,  
20 *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl;  
or a pharmaceutically acceptable salt thereof; with the proviso that said compound is not (*N*-methyl-*N*-butylsulphamoylmethyl)(phenyl)ketone; [1-(*N,N*-dimethylsulphamoyl)ethyl](phenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(4-nitrophenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(4-fluoro-2-methylaminophenyl)ketone;  
25 (*N,N*-dimethylsulphamoylmethyl)(3-methoxy-4-methyl-6-aminophenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(3-methoxy-6-aminophenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(phenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(2-nitro-4-methoxyphenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(2-amino-4-methoxyphenyl)ketone; [1-(*N*-methyl-*N*-butylsulphamoyl)ethyl](phenyl)ketone; or (*N,N*-dimethylsulphamoylmethyl)(thien-2-yl)ketone.

In this specification the term "alkyl" includes both straight and branched chain alkyl groups but references to individual alkyl groups such as "propyl" are specific for the straight chain version only. For example, "C<sub>1-4</sub>alkyl" includes propyl, isopropyl and *t*-butyl. However,

references to individual alkyl groups such as 'propyl' are specific for the straight chained version only and references to individual branched chain alkyl groups such as 'isopropyl' are specific for the branched chain version only. A similar convention applies to other radicals therefore "carbocyclC<sub>1-4</sub>alkyl" includes 1-carbocyclylpropyl, 2-carbocyclylethyl and 3-5 carbocyclylbutyl. The term "halo" refers to fluoro, chloro, bromo and iodo.

Where optional substituents are chosen from "one or more" groups it is to be understood that this definition includes all substituents being chosen from one of the specified groups or the substituents being chosen from two or more of the specified groups.

"Heteroaryl" is a totally unsaturated, mono or bicyclic ring containing 3-12 atoms of 10 which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Suitably "heteroaryl" refers to a totally unsaturated, monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 8 - 10 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked. Examples and suitable values of the 15 term "heteroaryl" are thienyl, furyl, thiazolyl, pyrazolyl, isoxazolyl, imidazolyl, pyrrolyl, thiadiazolyl, isothiazolyl, triazolyl, pyranyl, indolyl, pyrimidyl, pyrazinyl, pyridazinyl, benzothienyl, pyridyl and quinolyl. Particularly "heteroaryl" refers to thienyl, furyl, thiazolyl, pyridyl, benzothienyl, imidazolyl or pyrazolyl.

"Aryl" is a totally unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms. 20 Suitably "aryl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "aryl" include phenyl or naphthyl. Particularly "aryl" is phenyl.

A "heterocycl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 3-12 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH<sub>2</sub>- 25 group can optionally be replaced by a -C(O)- or a ring sulphur atom may be optionally oxidised to form the S-oxides. Preferably a "heterocycl" is a saturated, partially saturated or unsaturated, mono or bicyclic ring containing 5 or 6 atoms of which at least one atom is chosen from nitrogen, sulphur or oxygen, which may, unless otherwise specified, be carbon or nitrogen linked, wherein a -CH<sub>2</sub>- group can optionally be replaced by a -C(O)- or a ring 30 sulphur atom may be optionally oxidised to form S-oxide(s). Examples and suitable values of the term "heterocycl" are thienyl, piperidinyl, morpholinyl, furyl, thiazolyl, pyridyl, imidazolyl, 1,2,4-triazolyl, thiomorpholinyl, coumarinyl, pyrimidinyl, phthalidyl, pyrazolyl,

pyrazinyl, pyridazinyl, benzothienyl, benzimidazolyl, tetrahydrofuryl, [1,2,4]triazolo[4,3-a]pyrimidinyl, piperidinyl, indolyl, 1,3-benzodioxolyl and pyrrolidinyl.

A "carbocyclyl" is a saturated, partially saturated or unsaturated, mono or bicyclic carbon ring that contains 3-12 atoms; wherein a -CH<sub>2</sub>- group can optionally be replaced by a 5 -C(O)-. Preferably "carbocyclyl" is a monocyclic ring containing 5 or 6 atoms or a bicyclic ring containing 9 or 10 atoms. Suitable values for "carbocyclyl" include cyclopropyl, cyclobutyl, 1-oxocyclopentyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, phenyl, naphthyl, tetalinyl, indanyl or 1-oxoindanyl. Particularly "carbocyclyl" is cyclohexyl, phenyl, naphthyl or 2-6-dioxocyclohexyl.

10 An example of "C<sub>1-4</sub>alkanoyloxy" is acetoxy. Examples of "C<sub>1-4</sub>alkoxycarbonyl" include methoxycarbonyl, ethoxycarbonyl, *n*- and *t*-butoxycarbonyl. Examples of "C<sub>1-4</sub>alkoxy" include methoxy, ethoxy and propoxy. Examples of "oxyC<sub>1-4</sub>alkoxy" include oxymethoxy, oxyethoxy and oxypropoxy. Examples of "C<sub>1-4</sub>alkanoylamino" include formamido, acetamido and propionylamino. Examples of and "C<sub>1-4</sub>alkylS(O)<sub>a</sub> where a is 0 15 to 2" include methylthio, ethylthio, methylsulphinyl, ethylsulphinyl, mesyl and ethylsulphonyl. Examples of and "C<sub>1-4</sub>alkylsulphonyl" include mesyl and ethylsulphonyl. Examples of "C<sub>1-4</sub>alkanoyl" include propionyl and acetyl. Examples of "N-(C<sub>1-4</sub>alkyl)amino" include methylamino and ethylamino. Examples of "N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino" include di-*N*-methylamino, di-(*N*-ethyl)amino and *N*-ethyl-*N*-methylamino. Examples of 20 "C<sub>2-4</sub>alkenyl" are vinyl, allyl and 1-propenyl. Examples of "C<sub>2-4</sub>alkynyl" are ethynyl, 1-propynyl and 2-propynyl. Examples of "N-(C<sub>1-4</sub>alkyl)sulphamoyl" are *N*-(C<sub>1-3</sub>alkyl)sulphamoyl, *N*-(methyl)sulphamoyl and *N*-(ethyl)sulphamoyl. Examples of "N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl" are *N,N*-(dimethyl)sulphamoyl and *N*-(methyl)-*N*-(ethyl)sulphamoyl. Examples of "N-(C<sub>1-4</sub>alkyl)carbamoyl" are 25 methylaminocarbonyl and ethylaminocarbonyl. Examples of "N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl" are dimethylaminocarbonyl and methylethylaminocarbonyl. Examples of "C<sub>1-4</sub>alkylsulphonylamino" are mesylamino and ethylsulphonylamino. Examples of "C<sub>0-4</sub>alkylene" are a direct bond, methylene and ethylene. Examples of "tri-(C<sub>1-4</sub>alkyl)silyloxy" include tri-(methyl)silyloxy dimethyl-*t*-butylsilyloxy. Examples of 30 "C<sub>2-5</sub>alkylene" are propylene and butylene.

A suitable pharmaceutically acceptable salt of a compound of the invention is, for example, an acid-addition salt of a compound of the invention which is sufficiently basic, for example, an acid-addition salt with, for example, an inorganic or organic acid, for example

hydrochloric, hydrobromic, sulphuric, phosphoric, trifluoroacetic, citric or maleic acid. In addition a suitable pharmaceutically acceptable salt of a compound of the invention which is sufficiently acidic is an alkali metal salt, for example a sodium or potassium salt, an alkaline earth metal salt, for example a calcium or magnesium salt, an ammonium salt or a salt with an organic base which affords a physiologically-acceptable cation, for example a salt with methylamine, dimethylamine, trimethylamine, piperidine, morpholine or tris-(2-hydroxyethyl)amine.

Some compounds of the formula (I) may have chiral centres and/or geometric isomeric centres (E- and Z- isomers), and it is to be understood that the invention 10 encompasses all such optical, diastereoisomers and geometric isomers that possess 11 $\beta$ HSD1 inhibitory activity.

The invention relates to any and all tautomeric forms of the compounds of the formula (I) that possess 11 $\beta$ HSD1 inhibitory activity.

It is also to be understood that certain compounds of the formula (I) can exist in 15 solvated as well as unsolvated forms such as, for example, hydrated forms. It is to be understood that the invention encompasses all such solvated forms which possess 11 $\beta$ HSD1 inhibitory activity.

Particular values of variable groups are as follows. Such values may be used where appropriate with any of the definitions, claims or embodiments defined hereinbefore or 20 hereinafter.

Ring A is selected from aryl.

Ring A is heteroaryl.

Ring A is carbocyclyl.

Ring A is heterocyclyl.

25 Ring A is phenyl.

Ring A is pyridyl, phenyl, thienyl, furyl or pyrazinyl.

Ring A is pyrid-2-yl, phenyl, thien-2-yl, fur-2-yl, pyrazin-2-yl.

Ring A is pyridyl, phenyl, thienyl, furyl, pyrazinyl, 1,2,3-thiadiazolyl, thiazolyl, cyclohexyl, naphthyl, cyclohexenyl, pyrazolyl, benzothienyl, indolyl, 1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazolyl, 1,3-benzodioxolyl, cyclopentyl, tetrahydropyranyl, 1-oxooctahydropyrido[1,2-a]pyrazinyl, 1,2,3,4-tetrahydronaphthyl, piperidinyl and benzthiazolyl.

Ring A is pyrid-2-yl, pyrid-3-yl, phenyl, thien-2-yl, fur-2-yl, pyrazin-2-yl, 1,2,3-thiadiazol-5-yl, thiazol-2-yl, thiazol-5-yl, cyclohexyl, naphtha-2-yl, cyclohex-1-enyl, pyrazol-3-yl, benzothien-2-yl, indol-5-yl, 1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-6-yl, 1,3-benzodioxol-5-yl, cyclopentyl, tetrahydropyran-4-yl, 1-oxooctahydronpyrido[1,2-a]pyrazin-7-yl, 1,2,3,4-tetrahydronaphth-2-yl, piperidin-4-yl and benzthiazol-2-yl.

5 R<sup>1</sup> is selected from halo, cyano, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>1-4</sub>alkoxy or C<sub>1-4</sub>alkanoyl.

R<sup>1</sup> is selected from fluoro, chloro, cyano, methyl, 1-propenyl, methoxy or acetyl.

R<sup>1</sup> is selected from halo, nitro, cyano, sulphamoyl, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl,

C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, tri-(C<sub>1-4</sub>alkyl)silyloxy, carbocyclyl and heterocyclylC<sub>0-4</sub>alkylene-Y-;

10 wherein R<sup>1</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>.

R<sup>1</sup> is selected from fluoro, chloro, bromo, iodo, nitro, cyano, sulphamoyl, methyl, ethyl, t-butyl, allyl, ethynyl, methoxy, isopropoxy, acetyl, dimethyl-t-butylsilyloxy, phenyl and pyrimidin-4-ylamino; wherein R<sup>1</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>.

15 R<sup>1</sup> is selected from halo, nitro, cyano, sulphamoyl, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, tri-(C<sub>1-4</sub>alkyl)silyloxy, carbocyclyl and heterocyclylC<sub>0-4</sub>alkylene-Y-; wherein R<sup>1</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>; wherein

Y is -NR<sup>12</sup>-;

20 R<sup>12</sup> is hydrogen; and

R<sup>6</sup> is selected from halo, C<sub>2-4</sub>alkenyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoylamino and carbocyclyl.

R<sup>1</sup> is selected from fluoro, chloro, bromo, iodo, nitro, cyano, sulphamoyl, methyl, ethyl, t-butyl, allyl, ethynyl, methoxy, isopropoxy, acetyl, dimethyl-t-butylsilyloxy, phenyl

25 and pyrimidin-4-ylamino; wherein R<sup>1</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>; wherein

R<sup>6</sup> is selected from fluoro, chloro, ethenyl, acetyl, acetylamino and phenyl.

R<sup>1</sup> is selected from fluoro, chloro, bromo, iodo, nitro, cyano, sulphamoyl, methyl, allyl, t-butyl, ethynyl, methoxy, isopropoxy, acetyl, allyloxy, trifluoromethyl, phenyl,

30 benzyloxy, 4-chlorophenyl, 3-oxobutyl, 2-chloropyrimidin-4-yl, acetamidomethyl and dimethyl-t-butylsilyloxy.

Y is -NR<sup>12</sup>-.

R<sup>12</sup> is hydrogen.

R<sup>6</sup> is selected from halo, C<sub>2-4</sub>alkenyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoylamino and carbocyclyl.

R<sup>6</sup> is selected from fluoro, chloro, ethenyl, acetyl, acetylamino and phenyl.

When Ring A is phenyl, R<sup>1</sup> is selected from 2-fluoro, 3-fluoro, 4-fluoro, 2,4-difluoro, 5 3-chloro, 3-cyano, 4-cyano, 3-methyl, 3-(1-propenyl), 3-methoxy, 4-methoxy or 4-acetyl.

n is 0-3; wherein the values of R<sup>1</sup> may be the same or different.

n is 0-2; wherein the values of R<sup>1</sup> may be the same or different.

n is 0.

n is 1.

10 n is 2.

n is 3.

R<sup>1</sup>, n and Ring A together form phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3-iodophenyl, 4-iodophenyl, 3-methylphenyl, 4-t-butylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-isopropoxypyhenyl, 4-isopropoxypyhenyl, 3-cyanophenyl, 4-cyanophenyl, 4-trifluoromethylphenyl, 4-sulphamoylphenyl, 3-nitrophenyl, 4-nitrophenyl, 3-acetylphenyl, 4-acetylphenyl, 3-allylphenyl, 3-allyloxyphenyl, 4-allyloxyphenyl, 4-ethynylphenyl, 3-benzylxyphenyl, 4-benzylxyphenyl, 4-(3-oxobutyl)phenyl, 4-(dimethyl-t-butylsilyloxy)phenyl, 4-(2-chloropyrimidin-4-ylamino)phenyl, 4-(acetamidomethyl)phenyl, 2,4-difluorophenyl, 3,5-dimethylphenyl, 3,5-dibenzylxyphenyl, 3-methoxy-4-chlorophenyl, 3-fluoro-4-chlorophenyl, 3-cyano-4-methoxyphenyl, 3-ido-4-methoxyphenyl, 3-nitro-4-chlorophenyl, 3,4,5-trimethoxyphenyl, biphenyl-3-yl, biphenyl-4-yl, cyclohexyl, 6-cyanonaphth-2-yl, cyclohex-1-en-1-yl, cyclopentyl, 3-phenylcyclopentyl, pyrid-2-yl, 2-methylpyrid-5-yl, thien-2-yl, 5-chlorothien-2-yl, 3-chloro-4-methylthien-2-yl, fur-2-yl, 25 pyrazin-2-yl, 1,2,3-thiadiazol-5-yl, thiazol-2-yl, thiazol-5-yl, 4,5-dichlorothiazol-3-yl, 5-(4-chlorophenyl)pyrazol-3-yl, benzothien-2-yl, indol-5-yl, 1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-6-yl, 1,3-benzodioxol-5-yl, tetrahydropyran-4-yl, 1-oxooctahdropyrido[1,2-a]pyrazin-7-yl, 1,2,3,4-tetrahydronaphth-2-yl, 1-(pyrid-4-yl)piperidin-4-yl and benzothiazol-2-yl.

30 R<sup>1</sup>, n and Ring A together form phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3-iodophenyl, 4-iodophenyl, 3-methylphenyl, 4-methylphenyl, 4-t-butylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-isopropoxypyhenyl, 4-isopropoxypyhenyl, 3-cyanophenyl,

4-cyanophenyl, 4-trifluoromethylphenyl, 4-sulphamoylphenyl, 3-nitrophenyl, 4-nitrophenyl, 3-acetylphenyl, 4-acetylphenyl, 3-allylphenyl, 3-allyloxyphenyl, 4-allyloxyphenyl, 4-ethynylphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-(3-oxobutyl)phenyl, 4-(dimethyl-*t*-butylsilyloxy)phenyl, 4-(2-chloropyrimidin-4-ylamino)phenyl, 4-(acetamidomethyl)phenyl,  
5 2,4-difluorophenyl, 3,5-dimethylphenyl, 3,5-dibenzyloxyphenyl, 3-methoxy-4-chlorophenyl, 3-fluoro-4-chlorophenyl, 3-cyano-4-methoxyphenyl, 3-iodo-4-methoxyphenyl, 3-nitro-4-chlorophenyl, 3,4,5-trimethoxyphenyl, biphenyl-3-yl, biphenyl-4-yl, cyclohexyl, 6-cyanonaphth-2-yl, cyclohex-1-en-1-yl, cyclopentyl, 3-phenylcyclopentyl, pyrid-2-yl, 2-methylpyrid-5-yl, thien-2-yl, 5-chlorothien-2-yl, 3-chloro-4-methylthien-2-yl, fur-2-yl,  
10 pyrazin-2-yl, 1,2,3-thiadiazol-5-yl, thiazol-2-yl, thiazol-5-yl, 4,5-dichlorothiazol-3-yl, 5-(4-chlorophenyl)pyrazol-3-yl, benzothien-2-yl, indol-5-yl, 1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-6-yl, 1,3-benzodioxol-5-yl, tetrahydropyran-4-yl, 1-oxooctahydropsyrido[1,2-a]pyrazin-7-yl, 1,2,3,4-tetrahydronaphth-2-yl, 1-(pyrid-4-yl)piperidin-4-yl and benzothiazol-2-yl.

15  $R^2$  and  $R^3$  are both hydrogen.  
 $R^2$  and  $R^3$  are independently selected from hydrogen or C<sub>1-4</sub>alkyl.  
 $R^2$  and  $R^3$  are independently selected from hydrogen or C<sub>1-4</sub>alkyl, or  $R^2$  and  $R^3$  together form C<sub>2-6</sub>alkylene.  
 $R^2$  and  $R^3$  are independently selected from hydrogen or methyl.

20  $R^2$  and  $R^3$  are independently selected from hydrogen or methyl or  $R^2$  and  $R^3$  together form butylene.  
 $R^2$  and  $R^3$  are both hydrogen.  
 $R^2$  and  $R^3$  are both methyl.  
 $R^2$  and  $R^3$  together form butylene.

25 One of  $R^2$  and  $R^3$  is hydrogen and the other is methyl.  
 $R^4$  and  $R^5$  are independently selected from C<sub>1-4</sub>alkyl; wherein  $R^4$  and  $R^5$  may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>; and  
R<sup>10</sup> is selected from C<sub>1-4</sub>alkoxy and N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino.  
one of  $R^4$  and  $R^5$  is selected from hydrogen and C<sub>1-4</sub>alkyl and the other is selected from C<sub>1-4</sub>alkyl; wherein  $R^4$  and  $R^5$  may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>; and  
R<sup>10</sup> is selected from C<sub>1-4</sub>alkoxy and N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino.

one of R<sup>4</sup> and R<sup>5</sup> is selected from selected from hydrogen, methyl, isopropyl and ethyl, and the other is selected from methyl, isopropyl, propyl and ethyl; wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>.

R<sup>4</sup> and R<sup>5</sup> are independently selected from methyl, ethyl, propyl and isopropyl;

5 wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>; and

R<sup>10</sup> is selected from methoxy and N,N-dimethylamino.

one of R<sup>4</sup> and R<sup>5</sup> is selected from selected from hydrogen, methyl, isopropyl and ethyl, and the other is selected from methyl, isopropyl, propyl and ethyl; wherein R<sup>4</sup> and R<sup>5</sup> may be 10 optionally substituted on carbon by one or more groups selected from R<sup>10</sup>; and

R<sup>10</sup> is selected from methoxy, isopropoxy and N,N-dimethylamino.

R<sup>4</sup> and R<sup>5</sup> are independently selected from methyl, ethyl, 2-methoxyethyl, 2-(N,N-dimethylamino)propyl and isopropyl.

one of R<sup>4</sup> and R<sup>5</sup> is selected from selected from hydrogen, methyl, isopropyl and ethyl;

15 and the other is selected from methyl, isopropyl, propyl, 2-methoxyethyl, 2-dimethylaminoethyl, 2-(isopropoxy)ethyl and ethyl.

R<sup>10</sup> is selected from C<sub>1-4</sub>alkoxy and N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino.

R<sup>10</sup> is selected from methoxy, isopropoxy and N,N-dimethylamino.

R<sup>4</sup> and R<sup>5</sup> together with the nitrogen to which they are attached form isopropylamino,

20 dimethylamino, diethylamino, diisopropylamino, N-(methyl)-N-(propyl)amino, N-(methyl)-N-(isopropyl)amino, N-(methyl)-N-(2-methoxyethyl)amino, N-(isopropyl)-N-(2-methoxyethyl)amino, N-(isopropyl)-N-[2-(isopropoxy)ethyl]amino, N-(methyl)-N-(2-dimethylaminoethyl)amino and N-(ethyl)-N-(isopropyl)amino.

Therefore in a further aspect of the invention there is provided the use of a compound

25 of formula (I) (as depicted above) wherein:

Ring A is pyridyl, phenyl, thienyl, furyl or pyrazinyl;

R<sup>1</sup> is selected from halo, cyano, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>1-4</sub>alkoxy or C<sub>1-4</sub>alkanoyl;

n is 0-2; wherein the values of R<sup>1</sup> may be the same or different;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen or C<sub>1-4</sub>alkyl;

30 R<sup>4</sup> and R<sup>5</sup> are independently selected from C<sub>1-4</sub>alkyl; wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>; and

R<sup>10</sup> is selected from C<sub>1-4</sub>alkoxy and N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of  $11\beta$ HSD1.

Therefore in a further aspect of the invention there is provided the use of a compound of formula (I) (as depicted above) wherein:

Ring A is pyrid-2-yl, phenyl, thien-2-yl, fur-2-yl, pyrazin-2-yl;

5 R<sup>1</sup> is selected from fluoro, chloro, cyano, methyl, 1-propenyl, methoxy or acetyl;

n is 0-2; wherein the values of R<sup>1</sup> may be the same or different;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen or methyl;

10 R<sup>4</sup> and R<sup>5</sup> are independently selected from methyl, ethyl, 2-methoxyethyl, 2-(N,N-dimethylamino)propyl and isopropyl;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of  $11\beta$ HSD1.

Therefore in a further aspect of the invention there is provided the use of a compound of formula (I) (as depicted above) wherein:

Ring A is carbocyclyl or heterocyclyl;

15 R<sup>1</sup> is selected from halo, nitro, cyano, sulphamoyl, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, tri-(C<sub>1-4</sub>alkyl)silyloxy, carbocyclyl and heterocyclylC<sub>0-4</sub>alkylene-Y-; wherein R<sup>1</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>; wherein:

Y is -NR<sup>12</sup>-;

20 R<sup>12</sup> is hydrogen; and

R<sup>6</sup> is selected from halo, C<sub>2-4</sub>alkenyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoylamino and carbocyclyl;

n is 0-3; wherein the values of R<sup>1</sup> may be the same or different;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen or C<sub>1-4</sub>alkyl;

25 one of R<sup>4</sup> and R<sup>5</sup> is selected from hydrogen and C<sub>1-4</sub>alkyl and the other is selected from C<sub>1-4</sub>alkyl; wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>; and

R<sup>10</sup> is selected from C<sub>1-4</sub>alkoxy and N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino;

or a pharmaceutically acceptable salt thereof;

30 in the manufacture of a medicament for use in the inhibition of  $11\beta$ HSD1.

Therefore in a further aspect of the invention there is provided the use of a compound of formula (I) (as depicted above) wherein:

R<sup>1</sup>, n and Ring A together form phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3-iodophenyl, 4-iodophenyl, 3-methylphenyl, 4-t-butylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-isopropoxyphephenyl, 4-isopropoxyphephenyl, 3-cyanophenyl, 4-cyanophenyl, 4-trifluoromethylphenyl, 4-sulphamoylphenyl, 3-nitrophenyl, 4-nitrophenyl, 3-acetylphenyl, 4-acetylphenyl, 3-allylphenyl, 3-allyloxyphenyl, 4-allyloxyphenyl, 4-ethynylphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-(3-oxobutyl)phenyl, 4-(dimethyl-t-butylysilyloxy)phenyl, 4-(2-chloropyrimidin-4-ylamino)phenyl, 4-(acetamidomethyl)phenyl, 2,4-difluorophenyl, 3,5-dimethylphenyl, 3,5-dibenzyloxyphenyl, 3-methoxy-4-chlorophenyl, 3-fluoro-4-chlorophenyl, 3-cyano-4-methoxyphenyl, 3-iodo-4-methoxyphenyl, 3-nitro-4-chlorophenyl, 3,4,5-trimethoxyphenyl, biphenyl-3-yl, biphenyl-4-yl, cyclohexyl, 6-cyanonaphth-2-yl, cyclohex-1-en-1-yl, cyclopentyl, 3-phenylcyclopentyl, pyrid-2-yl, 2-methylpyrid-5-yl, thien-2-yl, 5-chlorothien-2-yl, 3-chloro-4-methylthien-2-yl, fur-2-yl, pyrazin-2-yl, 1,2,3-thiadiazol-5-yl, thiazol-2-yl, thiazol-5-yl, 4,5-dichlorothiazol-3-yl, 5-(4-chlorophenyl)pyrazol-3-yl, benzothien-2-yl, indol-5-yl, 1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-6-yl, 1,3-benzodioxol-5-yl, tetrahydropyran-4-yl, 1-oxooctahydropyrido[1,2-a]pyrazin-7-yl, 1,2,3,4-tetrahydronaphth-2-yl, 1-(pyrid-4-yl)piperidin-4-yl and benzothiazol-2-yl;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen or methyl; and

R<sup>4</sup> and R<sup>5</sup> together with the nitrogen to which they are attached form isopropylamino, dimethylamino, diethylamino, diisopropylamino, N-(methyl)-N-(propyl)amino, N-(methyl)-N-(isopropyl)amino, N-(methyl)-N-(2-methoxyethyl)amino, N-(isopropyl)-N-(2-methoxyethyl)amino, N-(isopropyl)-N-[2-(isopropoxy)ethyl]amino, N-(methyl)-N-(2-dimethylaminoethyl)amino and N-(ethyl)-N-(isopropyl)amino;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11 $\beta$ HSD1.

Therefore in a further aspect of the invention there is provided the use of a compound of formula (I) (as depicted above) wherein:

Ring A is carbocyclyl or heterocyclyl;

R<sup>1</sup> is selected from halo, nitro, cyano, sulphamoyl, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, tri-(C<sub>1-4</sub>alkyl)silyloxy, carbocyclyl and heterocyclylC<sub>0-4</sub>alkylene-Y-; wherein R<sup>1</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>; wherein:

Y is  $-NR^{12}-$ ;

R<sup>12</sup> is hydrogen; and

R<sup>6</sup> is selected from halo, C<sub>2-4</sub>alkenyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoylamino and carbocyclyl;

5 n is 0-3; wherein the values of R<sup>1</sup> may be the same or different;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen or C<sub>1-4</sub>alkyl, or R<sup>2</sup> and R<sup>3</sup> together form C<sub>2-6</sub>alkylene;

one of R<sup>4</sup> and R<sup>5</sup> is selected from hydrogen and C<sub>1-4</sub>alkyl and the other is selected from C<sub>1-4</sub>alkyl; wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more

10 groups selected from R<sup>10</sup>; and

R<sup>10</sup> is selected from C<sub>1-4</sub>alkoxy and N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino;

or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11 $\beta$ HSD1.

Therefore in a further aspect of the invention there is provided the use of a compound  
15 of formula (I) (as depicted above) wherein:

R<sup>1</sup>, n and Ring A together form phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 3-chlorophenyl, 4-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3-iodophenyl, 4-iodophenyl, 3-methylphenyl, 4-methylphenyl, 4-t-butylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3-isopropoxyphenyl, 4-isopropoxyphenyl, 3-cyanophenyl,

20 4-cyanophenyl, 4-trifluoromethylphenyl, 4-sulphamoylphenyl, 3-nitrophenyl, 4-nitrophenyl, 3-acetylphenyl, 4-acetylphenyl, 3-allylphenyl, 3-allyloxyphenyl, 4-allyloxyphenyl, 4-ethynylphenyl, 3-benzyloxyphenyl, 4-benzyloxyphenyl, 4-(3-oxobutyl)phenyl, 4-(dimethyl-t-butylsilyloxy)phenyl, 4-(2-chloropyrimidin-4-ylamino)phenyl, 4-(acetamidomethyl)phenyl, 2,4-difluorophenyl, 3,5-dimethylphenyl, 3,5-dibenzyloxyphenyl, 3-methoxy-4-chlorophenyl,

25 3-fluoro-4-chlorophenyl, 3-cyano-4-methoxyphenyl, 3-ido-4-methoxyphenyl, 3-nitro-4-chlorophenyl, 3,4,5-trimethoxyphenyl, biphenyl-3-yl, biphenyl-4-yl, cyclohexyl, 6-

cyanonaphth-2-yl, cyclohex-1-en-1-yl, cyclopentyl, 3-phenylcyclopentyl, pyrid-2-yl, 2-methylpyrid-5-yl, thien-2-yl, 5-chlorothien-2-yl, 3-chloro-4-methylthien-2-yl, fur-2-yl,

pyrazin-2-yl, 1,2,3-thiadiazol-5-yl, thiazol-2-yl, thiazol-5-yl, 4,5-dichlorothiazol-3-yl, 5-(4-

30 chlorophenyl)pyrazol-3-yl, benzothien-2-yl, indol-5-yl, 1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazol-6-yl, 1,3-benzodioxol-5-yl, tetrahydropyran-4-yl, 1-oxooctahdropyrido[1,2-a]pyrazin-7-yl, 1,2,3,4-tetrahydronaphth-2-yl, 1-(pyrid-4-yl)piperidin-4-yl and benzothiazol-2-yl.

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$R^2$  and  $R^3$  are independently selected from hydrogen or methyl or  $R^2$  and  $R^3$  together form butylene;

$R^4$  and  $R^5$  together with the nitrogen to which they are attached form isopropylamino, dimethylamino, diethylamino, diisopropylamino,  $N$ -(methyl)- $N$ -(propyl)amino,  $N$ -(methyl)- $N$ -(isopropyl)amino,  $N$ -(methyl)- $N$ -(2-methoxyethyl)amino,  $N$ -(isopropyl)- $N$ -(2-methoxyethyl)amino,  $N$ -(isopropyl)- $N$ -[2-(isopropoxy)ethyl]amino,  $N$ -(methyl)- $N$ -(2-dimethylaminoethyl)amino and  $N$ -(ethyl)- $N$ -(isopropyl)amino; or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of  $11\beta$ HSD1.

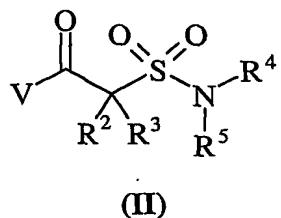
10 In another aspect of the invention, preferred compounds of the invention are any one of the Examples or a pharmaceutically acceptable salt thereof.

In another aspect of the invention, preferred compounds of the invention are Examples 2, 8, 12, 14, 31, 35, 55, 75 or 82, or a pharmaceutically acceptable salt thereof.

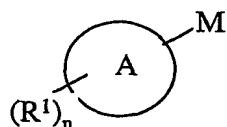
15 In another aspect of the invention, preferred compounds of the invention are any one of the Reference Examples or a pharmaceutically acceptable salt thereof.

Another aspect of the present invention provides a process for preparing a compound of formula (I) or (Ia) or a pharmaceutically acceptable salt thereof which process (wherein variable groups are, unless otherwise specified, as defined in formula (I) or (Ia)) comprises of:

20 *Process 1): reacting a compound of formula (II):*



wherein V is a displaceable group; with an organometallic reagent of formula (III):

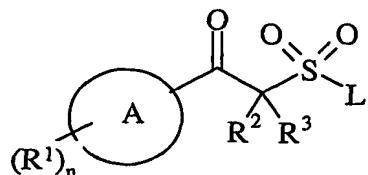


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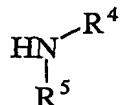
wherein M is a metal reagent;

*Process 2): reacting a compound of formula (IV):*

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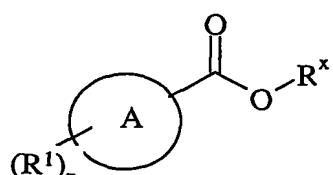


wherein L is a displaceable group; with an amine of formula (V):

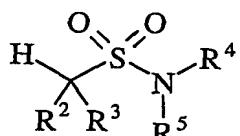


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*Process 3): reacting a compound of formula (VI):*

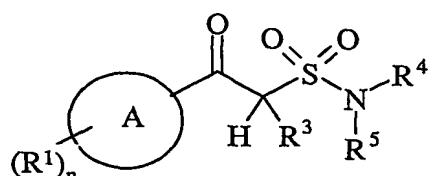


wherein RxOC(O)- is an ester with a compound of formula (VII):



10

*Process 4): for compounds of formula (I) wherein R<sup>2</sup> is not hydrogen; deprotonating a compound of formula (VIII):*



15

and reacting with a compound of formula (IX):



wherein R<sup>2</sup> is not hydrogen and L is a displaceable group;

20 and thereafter if necessary or desirable:

- i) converting a compound of the formula (I) into another compound of the formula (I);

- ii) removing any protecting groups;
- iii) forming a pharmaceutically acceptable salt thereof.

L is a displaceable group, suitable values for L include halo, particularly fluoro or chloro.

5 V is a displaceable group, suitable values for V include the Weinreb amide *N*-methyl-*N*-methoxyamine.

M is a metal reagent. Suitable values for M include Grignard reagents such as MgBr and lithium.

The group R<sup>x</sup>OC(O)- is an ester. Suitable values for R<sup>x</sup> are methyl and ethyl.

10 The reactions described above may be performed under standard conditions. The intermediates described above are commercially available, are known in the art or may be prepared by known procedures.

It will be appreciated that certain of the various ring substituents in the compounds of the present invention may be introduced by standard aromatic substitution reactions or

15 generated by conventional functional group modifications either prior to or immediately following the processes mentioned above, and as such are included in the process aspect of the invention. Such reactions and modifications include, for example, introduction of a substituent by means of an aromatic substitution reaction, reduction of substituents, alkylation of substituents and oxidation of substituents. The reagents and reaction conditions for such  
20 procedures are well known in the chemical art. Particular examples of aromatic substitution reactions include the introduction of a nitro group using concentrated nitric acid, the introduction of an acyl group using, for example, an acyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts conditions; the introduction of an alkyl group using an alkyl halide and Lewis acid (such as aluminium trichloride) under Friedel Crafts  
25 conditions; and the introduction of a halogeno group. Particular examples of modifications include the reduction of a nitro group to an amino group by for example, catalytic hydrogenation with a nickel catalyst or treatment with iron in the presence of hydrochloric acid with heating; oxidation of alkylthio to alkylsulphinyl or alkylsulphonyl.

It will also be appreciated that in some of the reactions mentioned herein it may be  
30 necessary/desirable to protect any sensitive groups in the compounds. The instances where protection is necessary or desirable and suitable methods for protection are known to those skilled in the art. Conventional protecting groups may be used in accordance with standard practice (for illustration see T.W. Green, Protective Groups in Organic Synthesis, John Wiley

and Sons, 1991). Thus, if reactants include groups such as amino, carboxy or hydroxy it may be desirable to protect the group in some of the reactions mentioned herein.

A suitable protecting group for an amino or alkylamino group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an alkoxycarbonyl group, for example a methoxycarbonyl, ethoxycarbonyl or *t*-butoxycarbonyl group, an arylmethoxycarbonyl group, for example benzyloxycarbonyl, or an aroyl group, for example benzoyl. The deprotection conditions for the above protecting groups necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or alkoxycarbonyl group or an aroyl group may be removed for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an acyl group such as a *t*-butoxycarbonyl group may be removed, for example, by treatment with a suitable acid as hydrochloric, sulphuric or phosphoric acid or trifluoroacetic acid and an arylmethoxycarbonyl group such as a benzyloxycarbonyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon, or by treatment with a Lewis acid for example boron tris(trifluoroacetate). A suitable alternative protecting group for a primary amino group is, for example, a phthaloyl group which may be removed by treatment with an alkylamine, for example dimethylaminopropylamine, or with hydrazine.

A suitable protecting group for a hydroxy group is, for example, an acyl group, for example an alkanoyl group such as acetyl, an aroyl group, for example benzoyl, or an arylmethyl group, for example benzyl. The deprotection conditions for the above protecting groups will necessarily vary with the choice of protecting group. Thus, for example, an acyl group such as an alkanoyl or an aroyl group may be removed, for example, by hydrolysis with a suitable base such as an alkali metal hydroxide, for example lithium or sodium hydroxide. Alternatively an arylmethyl group such as a benzyl group may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

A suitable protecting group for a carboxy group is, for example, an esterifying group, for example a methyl or an ethyl group which may be removed, for example, by hydrolysis with a base such as sodium hydroxide, or for example a *t*-butyl group which may be removed, for example, by treatment with an acid, for example an organic acid such as trifluoroacetic acid, or for example a benzyl group which may be removed, for example, by hydrogenation over a catalyst such as palladium-on-carbon.

The protecting groups may be removed at any convenient stage in the synthesis using conventional techniques well known in the chemical art.

As stated hereinbefore the compounds defined in the present invention possess 11 $\beta$ HSD1 inhibitory activity. These properties may be assessed using the following assay.

Assay

HeLa cells (human cervical carcinoma derived cells) were stably transfected with a construct containing four copies of the glucocorticoid response element (GRE) linked to a beta-galactosidase reporter gene (3 kb lac Z gene derived from pSV-B-galactosidase). These cells were then further stably transfected with a construct containing full-length human 11 $\beta$ HSD1 enzyme (in pCMVHyg) to create GRE4- $\beta$ Gal/11 $\beta$ HSD1 cells. The principal of the assay is as follows. Cortisone is freely taken up by the cells and is converted to cortisol by 11 $\beta$ HSD1 oxo-reductase activity and cortisol (but not cortisone) binds to and activates the glucocorticoid receptor. Activated glucocorticoid receptor then binds to the GRE and initiates transcription and translation of  $\beta$ -galactosidase. Enzyme activity can then be assayed with high sensitivity by colourimetric assay. Inhibitors of 11 $\beta$ HSD1 will reduce the conversion of cortisone to cortisol and hence decrease the production of  $\beta$ -galactosidase.

Cells were routinely cultured in DMEM (Invitrogen, Paisley, Renfrewshire, UK) containing 10% foetal calf serum (LabTech), 1% glutamine (Invitrogen), 1% penicillin & streptomycin (Invitrogen), 0.5 mg/ml G418 (Invitrogen) & 0.5mg/ml hygromycin (Boehringer). Assay media was phenol red free-DMEM containing 1% glutamine, 1% penicillin & streptomycin.

Compounds (1mM) to be tested were dissolved in dimethyl sulphoxide (DMSO) and serially diluted into assay media containing 10% DMSO. Diluted compounds were then plated into transparent flat-bottomed 384 well plates (Matrix, Hudson NH, USA).

The assay was carried out in 384 well microtitre plate (Matrix) in a total volume of 50 $\mu$ l assay media consisting of cortisone (Sigma, Poole, Dorset, UK, 1 $\mu$ M), HeLa GRE4- $\beta$ Gal/11 $\beta$ HSD1 cells (10,000 cells) plus test compounds (3000 to 0.01 nM). The plates were then incubated in 5% O<sub>2</sub>, 95% CO<sub>2</sub> at 37°C overnight.

The following day plates were assayed by measurement of  $\beta$ -galactosidase production. A cocktail (25 $\mu$ l) consisting of 10X Z-buffer (600 mM Na<sub>2</sub>HPO<sub>4</sub>, 400 mM NaH<sub>2</sub>PO<sub>4</sub>.2H<sub>2</sub>O, 100 mM KCl, 10 mM MgSO<sub>4</sub>.7H<sub>2</sub>O, 500 mM  $\beta$ -mercaptoethanol, pH 7.0), SDS (0.2%), chlorophenol red- $\beta$ -D-galactopyranoside (5mM, Roche Diagnostics) was added per well and plates incubated at 37°C for 3-4hours.  $\beta$ -Galactosidase activity was indicated by a yellow to red colour change (absorbance at 570nm) measured using a Tecan Spectrafluor Ultra.

The calculation of median inhibitory concentration ( $IC_{50}$ ) values for the inhibitors was performed using Origin 6.0 (Microcal Software, Northampton MA USA). Dose response curves for each inhibitor were plotted as OD units at each inhibitor concentration with relation to a maximum signal (cortisone, no compound) and  $IC_{50}$  values calculated. Compounds of the 5 present invention typically show an  $IC_{50} < 10\mu M$ . For example the following results were obtained:

Example	$IC_{50}$ (nM)
2	72
14	47
75	60

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula (Ia) or a pharmaceutically acceptable salt thereof, or a compound selected from Examples, or a pharmaceutically acceptable salt 10 thereof, as defined hereinbefore in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral administration, for example as a tablet or capsule, for parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion) as a sterile solution, suspension or emulsion, for topical 15 administration as an ointment or cream or for rectal administration as a suppository.

In general the above compositions may be prepared in a conventional manner using conventional excipients.

The compound of formula (I), or a pharmaceutically acceptable salt thereof, will normally be administered to a warm-blooded animal at a unit dose within the range 0.1 – 20 50 mg/kg that normally provides a therapeutically-effective dose. A unit dose form such as a tablet or capsule will usually contain, for example 1-1000 mg of active ingredient. However the daily dose will necessarily be varied depending upon the host treated, the particular route of administration, and the severity of the illness being treated. Accordingly the optimum dosage may be determined by the practitioner who is treating any particular patient.

25 We have found that the compounds defined in the present invention, or a pharmaceutically acceptable salt thereof, are effective  $11\beta$ HSD1inhibitors, and accordingly have value in the treatment of disease states associated with metabolic syndrome.

It is to be understood that where the term “metabolic syndrome” is used herein, this relates to metabolic syndrome as defined in 1) and/or 2) or any other recognised definition of

this syndrome. Synonyms for "metabolic syndrome" used in the art include Reaven's Syndrome, Insulin Resistance Syndrome and Syndrome X. It is to be understood that where the term "metabolic syndrome" is used herein it also refers to Reaven's Syndrome, Insulin Resistance Syndrome and Syndrome X.

5 According to a further aspect of the present invention there is provided a compound of the formula (Ia) or a pharmaceutically acceptable salt thereof, or a compound selected from Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

Thus according to this aspect of the invention there is provided a compound of the  
10 formula (Ia) or a pharmaceutically acceptable salt thereof, or a compound selected from Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore for use as a medicament.

According to another feature of the invention there is provided the use of a compound of the formula (Ia) or a pharmaceutically acceptable salt thereof, or a compound selected from  
15 the Examples, or a pharmaceutically acceptable salt thereof, as defined hereinbefore in the manufacture of a medicament for use in the production of an 11 $\beta$ HSD1 inhibitory effect in a warm-blooded animal, such as man.

According to another feature of the invention there is provided the use of a compound selected from Reference Examples, or a pharmaceutically acceptable salt thereof, as defined  
20 hereinbefore in the manufacture of a medicament for use in the production of an 11 $\beta$ HSD1 inhibitory effect in a warm-blooded animal, such as man.

Where production of or producing an 11 $\beta$ HSD1 inhibitory effect is referred to suitably this refers to the treatment of metabolic syndrome. Alternatively, where production of an 11 $\beta$ HSD1 inhibitory effect is referred to this refers to the treatment of diabetes, obesity,  
25 hyperlipidaemia, hyperglycaemia, hyperinsulinemia or hypertension, particularly diabetes and obesity. Alternatively, where production of an 11 $\beta$ HSD1 inhibitory effect is referred to this refers to the treatment of glaucoma, osteoporosis, tuberculosis, dementia, cognitive disorders or depression.

According to a further feature of this aspect of the invention there is provided a  
30 method for producing an 11 $\beta$ HSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof.

According to a further feature of this aspect of the invention there is provided a method for producing an  $11\beta$ HSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (Ia) or a pharmaceutically acceptable salt thereof, or a compound selected from Examples, or a pharmaceutically acceptable salt thereof.

According to a further feature of this aspect of the invention there is provided a method for producing an  $11\beta$ HSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound selected from the Reference Examples, or a pharmaceutically acceptable salt thereof.

In addition to their use in therapeutic medicine, the compounds of formula (I), or a pharmaceutically acceptable salt thereof, are also useful as pharmacological tools in the development and standardisation of *in vitro* and *in vivo* test systems for the evaluation of the effects of inhibitors of  $11\beta$ HSD1 in laboratory animals such as cats, dogs, rabbits, monkeys, rats and mice, as part of the search for new therapeutic agents.

The inhibition of  $11\beta$ HSD1 described herein may be applied as a sole therapy or may involve, in addition to the subject of the present invention, one or more other substances and/or treatments. Such conjoint treatment may be achieved by way of the simultaneous, sequential or separate administration of the individual components of the treatment.

Simultaneous treatment may be in a single tablet or in separate tablets. For example agents than might be co-administered with  $11\beta$ HSD1 inhibitors, particularly those of the present invention, may include the following main categories of treatment:

- 1) Insulin and insulin analogues;
- 2) Insulin secretagogues including sulphonylureas (for example glibenclamide, glipizide and prandial glucose regulators (for example repaglinide, nateglinide);
- 3) Insulin sensitising agents including PPAR $\gamma$  agonists (for example pioglitazone and rosiglitazone);
- 4) Agents that suppress hepatic glucose output (for example metformin);
- 5) Agents designed to reduce the absorption of glucose from the intestine (for example acarbose);
- 6) Agents designed to treat the complications of prolonged hyperglycaemia; e.g. aldose reductase inhibitors

- 7) Other anti-diabetic agents including phosphotyrosine phosphatase inhibitors, glucose 6 - phosphatase inhibitors, glucagon receptor antagonists, glucokinase activators, glycogen phosphorylase inhibitors, fructose 1,6 bisphosphatase inhibitors, glutamine:fructose -6-phosphate amidotransferase inhibitors
- 5 8) Anti-obesity agents (for example sibutramine and orlistat);
- 9) Anti- dyslipidaemia agents such as, HMG-CoA reductase inhibitors (statins, eg pravastatin); PPAR $\alpha$  agonists (fibrates, eg gemfibrozil); bile acid sequestrants (cholestyramine); cholesterol absorption inhibitors (plant stanols, synthetic inhibitors); ileal bile acid absorption inhibitors (IBATi), cholesterol ester transfer protein
- 10 inhibitors and nicotinic acid and analogues (niacin and slow release formulations);
- 11) Antihypertensive agents such as,  $\beta$  blockers (eg atenolol, inderal); ACE inhibitors (eg lisinopril); calcium antagonists (eg. nifedipine); angiotensin receptor antagonists (eg candesartan),  $\alpha$  antagonists and diuretic agents (eg. furosemide, benzthiazide);
- 12) Haemostasis modulators such as, antithrombotics, activators of fibrinolysis and antiplatelet agents; thrombin antagonists; factor Xa inhibitors; factor VIIa inhibitors); antiplatelet agents (eg. aspirin, clopidogrel); anticoagulants (heparin and Low molecular weight analogues, hirudin) and warfarin; and
- 13) Anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (eg. aspirin) and steroid anti-inflammatory agents (eg. cortisone).
- 20 In the above other pharmaceutical composition, process, method, use and medicament manufacture features, the alternative and preferred embodiments of the compounds of the invention described herein also apply.

#### Examples

The invention will now be illustrated in the following non limiting Examples, in which standard techniques known to the skilled chemist and techniques analogous to those described in these Examples may be used where appropriate, and in which, unless otherwise stated:

- (i) evaporation were carried out by rotary evaporation in vacuo and work up procedures were carried out after removal of residual solids such as drying agents by filtration;
- (ii) all reactions were carried out under an inert atmosphere at ambient temperature, typically in the range 18-25°C, with solvents of HPLC grade under anhydrous conditions, unless otherwise stated;
- (iii) column chromatography (by the flash procedure) was performed on Silica gel 40-63  $\mu\text{m}$  (Merck);

(iv) yields are given for illustration only and are not necessarily the maximum attainable;

(v) the structures of the end products of the formula (I) were generally confirmed by nuclear (generally proton) magnetic resonance (NMR) and mass spectral techniques; magnetic resonance chemical shift values were measured in deuterated  $\text{CDCl}_3$  (unless otherwise stated)

5 on the delta scale (ppm downfield from tetramethylsilane); proton data is quoted unless otherwise stated; spectra were recorded on a Varian Mercury-300 MHz, Varian Unity plus-400 MHz, Varian Unity plus-600 MHz or on Varian Inova-500 MHz spectrometer unless otherwise stated data was recorded at 400MHz; and peak multiplicities are shown as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; tt, triple triplet; q, quartet; tq, triple quartet;

10 m, multiplet; br, broad; ABq, AB quartet; ABd, AB doublet, ABdd, AB doublet of doublets; dABq, doublet of AB quartets; LCMS were recorded on a Waters ZMD, LC column xTerra MS C<sub>8</sub>(Waters), detection with a HP 1100 MS-detector diode array equipped; mass spectra (MS) (loop) were recorded on VG Platform II (Fisons Instruments) with a HP-1100 MS-detector diode array equipped; unless otherwise stated the mass ion quoted is ( $\text{MH}^+$ );

15 unless further details are specified in the text, analytical high performance liquid chromatography (HPLC) was performed on Prep LC 2000 (Waters), Cromasil C<sub>8</sub>, 7  $\mu\text{m}$ , (Akzo Nobel); MeCN and de-ionised water 10 mM ammonium acetate as mobile phases, with suitable composition;

(vii) intermediates were not generally fully characterised and purity was assessed by thin layer

20 chromatography (TLC), HPLC, infra-red (IR), MS or NMR analysis;

(viii) where solutions were dried magnesium sulphate was the drying agent;

(ix) where an "ISOLUTE" column is referred to, this means a column containing 2 g of silica, the silica being contained in a 6 ml disposable syringe and supported by a porous disc of 54 $\text{\AA}$  pore size, obtained from International Sorbent Technology under the name "ISOLUTE";

25 "ISOLUTE" is a registered trade mark;

(x) the following abbreviations may be used hereinbefore or hereinafter:-

DCM            dichloromethane;

EtOAc          ethyl acetate;

MeCN          acetonitrile; and

30 THF          tetrahydrofuran.

**Reference Example 1****(N,N-Dimethylsulphamoylmethyl)(phenyl)ketone**

The title compound was prepared by the procedure of J.Med.Chem.; EN; 30; 12; 1987; 2232-2239. Reference Example 1 is exemplified in this reference.

5

**Reference Example 2****(N,N-Dimethylsulphamoylmethyl)(4-fluorophenyl)ketone**

The title compound was prepared by the procedure of Reference Example 1. NMR: 2.9 (s, 6H), 4.5 (s, 2H), 7.2 (m, 2H), 8.0 (m, 2H); m/z 244.

10

**Reference Example 3****(N,N-Dimethylsulphamoylmethyl)(thien-2-yl)ketone**

To a stirred solution of methylthiophene-2-carboxylate (520mg, 3.65mmol) and *N,N*-dimethylmethanesulphonamide (375mg, 3.04mmol) in ethylene glycol dimethyl ether (15ml)

15 was added sodium hydride (60% suspension in oil, 328mg, 8.21mmol). The reaction was warmed to 85°C and stirred at this temperature overnight then cooled to room temperature and quenched with water. The resulting brown solution was acidified to ~pH2 with concentrated hydrochloric acid and then extracted with DCM (2 x 40ml). The organic layers were combined, washed with water (30ml) and brine (20ml) then dried, filtered and evaporated to 20 yield crude product. This was purified by column chromatography (20g Silica, eluting with DCM) to yield an oil which crystallised on standing. This material was still impure. The crude was product partitioned between DCM and 1M sodium hydroxide solution, the layers separated and the sodium hydroxide layer re extracted with DCM. The aqueous layer was then acidified to ~pH3 with concentrated HCl and then extracted with DCM twice. These two 25 DCM layers were combined, washed with brine, dried, filtered and evaporated to yield the product as a solid (56mg, 7%). NMR: 2.90 (s, 6H), 4.45 (s, 2H), 7.20 (m, 1H), 7.75 (m, 1H), 7.90 (m, 1H); m/z: 234.

**Reference Example 4****[1-(N,N-Dimethylsulphamoyl)ethyl](phenyl)ketone**

To a stirred solution of (*N,N*-dimethylsulphamoylmethyl)(phenyl)ketone (Reference Example 1; 88mg, 0.39mmol) in DMF (7ml) was added potassium carbonate (107mg, 0.78mmol) followed by methyl iodide (113mg, 0.8mmol). The resulting suspension was

stirred at room temperature for 2 hours. The reaction was quenched with water (~50ml) and extracted with DCM (2x50ml). The organic layers combined, dried, filtered and evaporated to yield the product as a yellow oil (still contains a trace of DMF). NMR: 1.70 (d, 3H), 2.90 (s, 6H), 5.15 (m, 1H), 7.50 (t, 2H), 7.60 (m, 2H), 8.00 (br m, 1H); m/z: 242.

5

### Example 1

#### [1-(N,N-Dimethylsulphamoyl)-1-methylethyl](phenyl)ketone

To a stirred solution of [1-(N,N-dimethylsulphamoyl)ethyl](phenyl)ketone (Refernece Example 4; 33mg, 0.14mmol) in DMF was added potassium carbonate (39mg, 0.28mmol) and methyl iodide (60mg, 0.42mmol). The reaction was warmed to 40°C and stirred at this temperature for 18 hours. Further methyl iodide was added (60mg, 0.42mmol) and the reaction was stirred at 40°C for a further 24 hours. The volatiles were removed under reduced pressure and the resulting crude product was partitioned between ether and 1M sodium hydroxide solution, the ether layer was separated and re-extracted with sodium hydroxide solution then washed with brine, dried, filtered and evaporated to yield the product as a clear oil (16mg, 43%). M/z: 256.

### Example 2

#### (N,N-Dimethylsulphamoylmethyl)(pyrid-2-yl)ketone

20 To a solution of *N*-dimethylmethysulphonamide (1.23 g, 10mmol) in THF (30ml), under an inert atmosphere at 0°C was added dropwise a solution of butyl lithium in hexanes 1.6M (12.5ml, 20mmol). After 30 minutes at 0°C, the mixture (white paste) was cooled to -78°C and ethylpicolinate (1.51g, 10mmol) in THF (5 ml) was added. After 1 hour, the cooling bath was removed and the temperature was allowed to warm to 0°C. The mixture was 25 diluted with cooled water and extracted twice with ether. The aqueous phase was acidified to pH 5 and extracted three times with EtOAc. The EtOAc extracts were combined and washed with brine, dried over, filtered and concentrated. The brown mauve resulting oil was triturated in ether until crystallisation occurred and the solid was filtered off (1.4 g , 66%). NMR: 2.92 (s, 6H), 4.98 (s, 2H), 7.55 (m, 1H), 7.89 (m, 1H), 8.11 (d, 1H), 8.74 (m, 1H); m/z: 229.

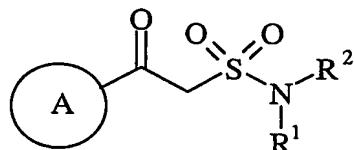
30

**Example 3****(N,N-Diisopropylsulphamoylmethyl)(4-fluorophenyl)ketone**

To a stirred solution of *N,N*-diisopropylmethansulphonamide (120mg, 0.67mmol) in anhydrous THF (3ml) at -20°C was added a 1M solution of lithium bis(trimethylsilyl)amide 5 in THF (1.34ml, 1.34mmol). The reaction was stirred at -20°C for 30 minutes and then a solution of methyl-4-flurobenzoate (134mg, 0.87mmol) in anhydrous THF (1ml) was added. The reaction was allowed to warm to room temperature over an hour then quenched with saturated ammonium chloride solution (5ml). The layers were separated and the aqueous layer was extracted with EtOAc. The THF and EtOAc extracts were combined, washed with brine, 10 dried, filtered and evaporated to yield an impure oil. The crude product was purified by column chromatography (eluting with DCM to 5%MeOH/DCM) to yield the product as an oil which crystallised on standing (70mg, 35%). NMR: 1.25 (d, 12H), 3.65 (m, 2H), 4.40 (s, 2H), 7.10 (t, 2H), 8.02 (m, 2H); m/z: 300 (M-H)<sup>-</sup>.

**15 Examples 4-76 and Reference Examples 5 and 6**

The procedure described in Example 3 was repeated using the appropriate reagent(s) in place of *N,N*-diisopropylmethanesulphonamide and/or methyl-4-flurobenzoate to give the following Examples. Where the methanesulphonamides were not known compounds or commercially available the preparation of the starting materials (SM) is indicated.



20

Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
4	3-Chloro phenyl	Me	Me	2.95 (s, 6H), 4.55 (s, 2H), 7.45 (t, 1H), 7.60 (m, 1H), 7.90 (m, 1H), 8.00 (m, 1H)	262	
5	4-Fluoro phenyl	Et	Et	1.20 (t, 6H), 3.30 (q, 4H), 4.50 (s, 2H), 7.15 (t, 2H), 8.10 (m, 2H)	274	<sup>2</sup>

Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
6	3-Methoxy phenyl	Me	Me	2.90 (s, 6H), 3.85 (s, 3H), 4.55 (s, 2H), 7.20 (m, 1H), 7.40 (t, 1H), 7.50 (m, 1H), 7.65 (m, 1H)	258	
7	Fur-2-yl	i-Pr	i-Pr	1.30 (d, 12H), 3.75 (m, 2H), 4.40 (s, 2H), 6.60 (m, 1H), 7.40 (m, 1H), 70 (m, 1H)	272 (M- H) <sup>-</sup>	<sup>3</sup>
8	4-Fluoro phenyl	Me	-(CH <sub>2</sub> ) <sub>2</sub> - OCH <sub>3</sub>	2.95 (s, 3H), 3.25 (s, 3H), 3.35 (q, 2H), 3.44 (q, 2H), 4.55 (s, 2H), 7.10 (t, 2H), 8.00 (m, 2H)	290	Meth 1
9	4-Fluoro phenyl	Me	Pr	0.90 (t, 3H), 1.60 (m, 2H), 2.90 (s, 3H), 3.15 (t, 2H), 4.55 (s, 2H), 7.15 (t, 2H), 8.10 (m, 2H)	274	Meth 2
10	4-Fluoro phenyl	Et	i-Pr	1.20 (t, 3H), 1.25 (d, 6H), 3.20 (q, 2H), 3.95 (m, 1H), 4.50 (s, 2H), 7.20 (t, 2H), 8.10 (m, 2H)	286 (M- H) <sup>-</sup>	Meth 3
11	4-Methoxy phenyl	Me	Me	2.90 (s, 6H), 3.90 (s, 3H), 3.55 (s, 2H), 7.00 (d, 2H), 8.00 (d, 2H)	258	
12	Thiazol-2-yl	Me	Me	2.90 (s, 6H), 4.85 (s, 2H), 7.80 (d, 1H), 8.10 (d, 1H)	233 (M- H) <sup>-</sup>	
13	1,2,3-Thia-diazol-5-yl	Me	Me	2.95 (s, 6H), 4.50 (s, 2H), 9.20 (s, 1H)	234 (M- H) <sup>-</sup>	
14	Pyrazin-2-yl	Me	Me	2.95 (s, 6H), 4.80 (s, 2H), 8.70 (m, 1H), 8.80 (d, 1H), 9.30 (s, 1H)	228 (M- H) <sup>-</sup>	

Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
15	4-Fluoro phenyl	Me	-(CH <sub>2</sub> ) <sub>2</sub> -N(Me) <sub>2</sub>	2.30 (s, 6H), 2.50 (t, 2H), 3.00 (br s, 3H), 3.35 (t, 2H), 4.70 (br s, 2H), 7.20 (br t, 3H), 8.10 (m, 2H)	303	Meth 6
16	Thiazol-5-yl	Me	Me	2.95 (s, 6H), 4.50 (s, 2H), 8.60 (s, 1H), 9.10 (s, 1H)	235	<sup>1</sup>
17 <sup>4,5</sup>	4-Trifluoro-methyl phenyl	Me	Me	2.9 (s, 6H), 4.6 (s, 2H), 7.8 (d, 2H), 8.2 (d, 2H)	294 (M-H) <sup>-</sup>	
18 <sup>4,5</sup>	4-t-Butylphenyl	Me	Me	1.6 (s, 9H), 2.9 (s, 6H), 4.6 (s, 2H), 7.6 (d, 2H), 8.0 (d, 2H)	282 (M-H) <sup>-</sup>	
19 <sup>4</sup>	6-Cyano naphth-2-yl	Me	Me		301 (M-H) <sup>-</sup>	
20 <sup>4,5</sup>	4-Chloro-3-fluorophenyl	Me	Me	2.9 (s, 6H), 4.6 (s, 2H), 7.6 (m, 1H), 7.8 (m, 2H)	278 (M-H) <sup>-</sup>	
21 <sup>4</sup>	3-Cyano-4-methoxy phenyl	Me	Me	2.9 (s, 6H), 4.1 (s, 3H), 4.5 (s, 2H), 7.1 (d, 1H), 8.3 (m, 2H)		
22 <sup>4,5</sup>	3-Iodo phenyl	Me	Me	2.9 (s, 6H), 4.5 (s, 2H), 7.3 (dd, 1H), 8.0 (m, 2H), 8.4 (d, 1H)	352 (M-H) <sup>-</sup>	
23 <sup>4,5</sup>	3-Iodo-4-methoxy phenyl	Me	Me	2.9 (s, 6H), 4.0 (s, 3H), 4.5 (s, 2H), 6.9 (d, 1H), 8.0 (dd, 1H), 8.4 (d, 2H)	382 (M-H) <sup>-</sup>	
24 <sup>4,5</sup>	3-Bromo phenyl	Me	Me	2.9 (s, 6H), 4.5 (s, 2H), 7.4 (t, 1H), 7.7 (dd, 1H), 8.0 (dd, 1H), 8.2 (d, 1H)	306 (M-H) <sup>-</sup>	
25 <sup>4,5</sup>	Biphen-4-yl	Me	Me		302 (M-H) <sup>-</sup>	

Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
26 <sup>4,</sup> 5	3,5-Dimethyl phenyl	Me	Me		254 (M-H) <sup>-</sup>	
27 <sup>4,</sup> 5	3,5-Dibenzylxy phenyl	Me	Me		438 (M-H) <sup>-</sup>	
RE 5 <sup>4,5</sup>	4-Nitro phenyl	Me	Me		271 (M-H) <sup>-</sup>	
28 <sup>4,</sup> 5	3-Nitro phenyl	Me	Me		271 (M-H) <sup>-</sup>	
29 <sup>4,</sup> 5	3-Nitro-4-chlorophenyl	Me	Me		305 (M-H) <sup>-</sup>	
30 <sup>4,</sup> 5	6-Methyl pyrid-3-yl	Me	Me		241 (M-H) <sup>-</sup>	
31 <sup>6</sup>	2,4-Difluoro phenyl	i-Pr	i-Pr	d <sup>6</sup> -DMSO, 1.22 (d, 12H), 3.75 (m, 2H), 4.65 (s, 2H), 7.24 (m, 1H), 7.42 (m, 1H), 8.00 (m, 1H)	318 (M-H) <sup>-</sup>	<sup>3</sup>
32 <sup>6</sup>	4-Bromo phenyl	Me	Me	d <sup>6</sup> -DMSO, 2.82 (s, 6H), 4.92 (s, 2H), 7.77 (d, 2H), 7.96 (d, 2H)	304 (M-H) <sup>-</sup>	
33 <sup>6</sup>	4-Iodo phenyl	Me	Me	d <sup>6</sup> -DMSO, 2.80 (s, 6H), 4.88 (s, 2H), 7.78 (d, 2H), 7.95 (d, 2H)	354	
34 <sup>6</sup>	3-(Allyloxy) phenyl	Me	Me	d <sup>6</sup> -DMSO, 2.81 (s, 6H), 4.63 (m, 2H), 4.90 (s, 2H), 5.27 (m, 1H), 5.41 (m, 1H), 6.05 (m, 1H), 7.27 (m, 1H), 7.46 (m, 1H), 7.54 (m, 1H), 7.63 (m, 1H)	284	

Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
35 <sup>4,</sup> 7	3-Cyano phenyl	i-Pr	i-Pr		307 (M- H) <sup>-</sup>	<sup>3</sup>
36 <sup>4,</sup> 7	Phenyl	i-Pr	i-Pr		282 (M- H) <sup>-</sup>	<sup>3</sup>
37 <sup>4,</sup> 6	1,3-Benzo- dioxol-5-yl	i-Pr	i-Pr	d <sup>6</sup> -DMSO, 1.22 (d, 12H), 3.74 (m, 2H), 4.66 (s, 2H), 6.15 (s, 2H), 7.04 (d, 1H), 7.46 (d, 1H), 7.66 (dd, 1H)	326 (M- H) <sup>-</sup>	<sup>3</sup>
38 <sup>4,</sup> 7	4-Cyano phenyl	i-Pr	i-Pr		307 (M- H) <sup>-</sup>	<sup>3</sup>
39 <sup>4,</sup> 6	4- (Acetamido- methyl) phenyl	i-Pr	i-Pr		353 (M- H) <sup>-</sup>	<sup>3</sup>
40 <sup>4,</sup> 7,	1,1,3- Trioxo-2,3- dihydro-1,2- benziso- thiazol-6-yl	i-Pr	i-Pr		387 (M- H) <sup>-</sup>	<sup>3,9</sup>
41 <sup>4,</sup> 7	1 <i>H</i> -indol-5- yl	i-Pr	i-Pr	d <sup>6</sup> -DMSO, 1.23 (d, 12H), 3.76 (m, 2H), 4.72 (s, 2H), 6.63 (m, 1H), 7.14 (br s, 1H), 7.47 (m, 2H), 7.76 (m, 1H), 8.38 (m, 1H)	321 (M- H) <sup>-</sup>	<sup>3</sup>
42 <sup>4,</sup> 7	4- (Benzloxy) phenyl	Me	Me	d <sup>6</sup> -DMSO, 2.79 (s, 6H), 4.81 (s, 2H), 5.23 (s, 2H), 7.15 (d, 2H), 7.41 (m, 5H), 8.00 (d, 2H)	334	
43 <sup>4,</sup> 6	Biphen-3-yl	Me	Me		304	

Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
44 <sup>4,6</sup>	3-Acetyl phenyl	Me	Me	d <sup>6</sup> -DMSO, 2.64 (s, 3H), 2.83 (s, 6H), 5.00 (s, 2H), 7.71 (m, 1H), 8.24 (m, 2H), 8.50 (m, 1H)	270	
45 <sup>4,6</sup>	3-(Benzylxy) phenyl	Me	Me		332 (M-H) <sup>-</sup>	
46 <sup>4,6</sup>	4,5-Dichloro thiazol-2-yl	Me	Me	d <sup>6</sup> -DMSO, 2.83 (s, 6H), 4.88 (s, 2H)	303 (M-H) <sup>-</sup>	
47 <sup>4,6</sup>	Benzothien-2-yl	Me	Me	d <sup>6</sup> -DMSO, 2.84 (s, 6H), 4.95 (s, 2H), 7.53 (m, 2H), 8.06 (m, 2H), 8.57 (s, 1H)	282 (M-H) <sup>-</sup>	
48 <sup>4,6</sup>	2-Chloro thien-5-yl	Me	Me		266 (M-H) <sup>-</sup>	
49 <sup>4,6</sup>	3-Chloro-4-methylthien-2-yl	Me	Me	d <sup>6</sup> -DMSO, 2.21 (s, 3H), 2.84 (s, 6H), 4.79 (s, 2H), 7.92 (s, 1H)	280 (M-H) <sup>-</sup>	
50 <sup>4,6</sup>	5-(4-Chloro phenyl) pyrazol-3-yl	Me	Me		326 (M-H) <sup>-</sup>	<sup>10</sup>
51 <sup>4,5</sup>	4-(3-Oxobutyl) phenyl	Me	Me		296	
52 <sup>4,5</sup>	4-(2-Chloro pyrimidin-4-ylamino) phenyl	Me	Me	d <sup>6</sup> -DMSO, 2.81 (s, 6H), 4.82 (s, 2H), 6.90 (d, 1H), 7.81 (d, 2H), 8.05 (d, 2H), 8.27 (d, 2H), 10.48 (br s, 1H)	355	
53 <sup>4,5</sup>	4-Sulphamoyl phenyl	Me	Me	d <sup>6</sup> -DMSO, 2.81 (s, 6H), 4.98 (s, 2H), 7.57 (s, 2H), 7.96 (d, 2H), 8.22 (d, 2H)	305 (M-H) <sup>-</sup>	

Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
54 <sup>4</sup> , 8	Benzothien-2-yl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> -O-iPr		382 (M-H) <sup>-</sup>	Meth 11
55 <sup>4</sup> , 8	4-Fluoro phenyl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> -O-iPr		344 (M-H) <sup>-</sup>	Meth 11
56 <sup>4</sup> , 8	2,4-Difluoro phenyl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> -O-iPr		362 (M-H) <sup>-</sup>	Meth 11
57 <sup>4</sup> , 8	2-Chloro thien-5-yl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> -O-iPr		366 (M-H) <sup>-</sup>	Meth 11
58 <sup>4</sup> , 8	Thiazol-2-yl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> -O-iPr		333 (M-H) <sup>-</sup>	Meth 11
59 <sup>4</sup> , 8	4-Fluoro phenyl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>3</sub>		316 (M-H) <sup>-</sup>	Meth 10
60 <sup>4</sup> , 8	2-Chloro thien-5-yl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>3</sub>		338 (M-H) <sup>-</sup>	Meth 10
61 <sup>4</sup> , 8	2,4-Difluoro phenyl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> OCH <sub>3</sub>		334 (M-H) <sup>-</sup>	Meth 10
62	4-( <i>t</i> -Butyl dimethyl silyloxy) phenyl	i-Pr	i-Pr	0.27 (s, 6H), 1.00 (s, 9H), 1.33 (d, 12H), 3.73 (m, 2H), 4.47 (s, 2H), 6.90 (d, 2H), 7.99 (d, 2H)		11
RE 6 <sup>4,5</sup>	Cyclohexyl	Me	Me	1.3 (m, 5H), 1.7 (d, 1H), 1.8 (b, 2H), 1.9 (b, 2H), 2.7 (m, 1H), 2.9 (s, 6H), 4.0 (s, 2H)		
63 <sup>4</sup>	Cyclohex-1-en-1-yl	Me	Me		232 (M+H) <sup>+</sup>	
64 <sup>7</sup>	3-Phenyl cyclopentyl	Me	Me	d <sup>6</sup> -DMSO, 1.80 (m, 6H), 2.27 (m, 1H), 2.80 (s, 6H), 3.04 (m, 1H), 4.37 (s, 2H), 7.22 (m, 5H)		

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Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
65 <sup>7</sup>	1,2,3,4-Tetrahydro naphth-2-yl	Me	Me	d <sup>6</sup> -DMSO, 1.62 (m, 1H), 2.14 (m, 1H), 2.80 (s, 6H), 2.93 (m, 5H), 4.50 (m, 2H), 7.07 (m, 4H)		
66 <sup>7</sup>	Cyclopentyl	Me	Me	d <sup>6</sup> -DMSO, 1.54 (m, 4H), 1.66 (m, 2H), 1.80 (m, 2H), 2.77 (s, 6H), 3.10 (m, 1H), 4.34 (s, 2H)		
67 <sup>7</sup>	1-(Pyrid-4-yl)-piperidin-4-yl	Me	Me	d <sup>6</sup> -DMSO, 1.43 (m, 2H), 1.92 (m, 2H), 2.78 (s, 6H), 2.90 (m, 3H), 3.92 (m, 2H), 4.42 (s, 2H), 6.80 (m, 2H), 8.12 (m, 2H)		
68 <sup>7</sup>	4-Tetrahyro pyran-4-yl	Me	Me	d <sup>6</sup> -DMSO, 1.43 (m, 2H), 1.77 (m, 2H), 2.77 (s, 6H), 2.86 (m, 1H), 3.33 (m, 2H), 3.85 (m, 2H), 4.39 (s, 2H)		
69 <sup>7</sup>	1-Oxo octahydro pyrido[1,2-a]pyrazin-7-yl	Me	Me	d <sup>6</sup> -DMSO, 1.23 (m, 2H), 2.05 (m, 2H), 2.16 (m, 1H), 2.37 (m, 2H), 2.76 (s, 6H), 2.86 (m, 2H), 3.05 (m, 2H), 3.22 (m, 1H), 4.40 (m, 2H), 7.60 (br s, 1H)		
70	Benzothien-2-yl	i-Pr	i-Pr	1.30-1.23 (d, 6H); 3.68-3.84 (m, 2H); 4.56 (s, 2H); 7.37-7.53 (m, 2H); 7.83-7.90 (d, 1H); 7.91-7.99 (d, 1H); 8.22 (s, 1H)	+ve 340	<sup>3</sup>

Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
71	Benzthiazol-2-yl	i-Pr	i-Pr	1.26-1.45 (d, 12H); 3.74-3.94 (m, 2H); 4.92 (s, 2H); 7.50 (m, 2H); 7.93-8.02 (d, 1H); 8.17-8.27 (d, 1H)	+ve 341	<sup>3</sup>
72	3-Isopropoxyphenyl	i-Pr	i-Pr	1.28-1.45 (m, 18H); 3.67-3.83 (m, 2H); 4.51 (s, 2H); 4.55-4.69 (m, 1H); 7.08-7.16 (app dd, 1H); 7.33-7.43 (app t, 1H), 7.55 (m, 1H); 7.59-7.65 (d, 1H)	+ve 342	<sup>3</sup>
73	Thiazol-2-yl	i-Pr	i-Pr	1.23-1.43 (d, 12H); 3.72-3.91 (m, 2H); 4.80 (s, 2H); 7.71-7.79 (d, 1H); (8.03-8.10 (d, 1H)	+ve 291	<sup>3</sup>
74	4-Bromo phenyl	i-Pr	i-Pr	1.09-1.32 (d, 12H); 3.66-3.86 (m, 2H); 4.76 (s, 2H); 7.71-7.85 (d, 2H); 7.90-8.03 (d, 2H)	-ve 360	<sup>3</sup>
75	4-Isopropoxyphenyl	i-Pr	i-Pr	1.23-1.40 (d, 12H); 1.40-1.42 (d, 6H); 3.66-3.80 (m, 2H); 4.48 (s, 2H); 4.60-4.72 (m, 1H); 6.89-6.96 (d, 2H); 7.97-8.07 (d, 2H)	+ve 342	<sup>3</sup>
76 <sup>6</sup>	4-Methyl Phenyl	Me	Me	d <sup>6</sup> -DMSO, 2.40 (s, 3H), 2.80 (s, 6H), 4.84 (s, 2H), 7.36 (d, 2H), 7.92 (d, 2H)	242 (M+H) <sup>+</sup>	

<sup>1</sup> Starting ester prepared according to Tetrahedron Lett.; EN; 25; 51; 1984; 5939-5942

<sup>2</sup> Sulphonamide preparation: J.Amer.Chem.Soc.; 76; 1954; 303

<sup>3</sup> Sulphonamide preparation: Tetrahedron; EN; 25; 1969; 181-189

<sup>4</sup> Reaction carried out at room temperature overnight

<sup>5</sup> Product crystallised from EtOAc / hexane in place of chromatography.

<sup>6</sup>Purification by chromatography (eluting with 25% EtOAc/isohexane to 50% EtOAc/isohexane)

<sup>7</sup>Product triturated with diethyl ether.

<sup>8</sup>Purification by chromatography (eluting with 10% EtOAc/isohexane to 20%

5 EtOAc/isohexane)

<sup>9</sup>Starting ester prepared according to Azerbaidzhanskii Khimicheskii Zhurnal; 1997; 1-4; 62-66.

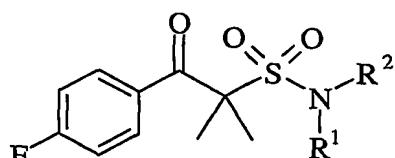
<sup>10</sup>Starting ester prepared according to PCT Int. Appl.; 1997; 99pp.; WO9721682.

<sup>11</sup>Starting ester prepared according to J. Org. Chem.; 1991; 56(16); 4884-7.

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### Examples 77-79

The procedure described in Example 3 was repeated using the appropriate reagent(s) in place of *N,N*-diisopropylmethanesulphonamide to give the following Examples.



Ex	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
77	Me	Me	1.73 (s, 6H), 2.93 (s, 6H), 7.10 (m, 2H), 8.05 (m, 2H)		Method 7
78	Me	i-Pr	1.12 (d, 6H), 1.62 (s, 6H), 2.68 (s, 3H), 3.87 (m, 1H), 7.30 (m, 2H), 7.94 (m, 2H)	302	Method 8
79	H	i-Pr	1.28 (d, 6H), 2.10 (s, 6H), 3.80 (m, 1H), 7.07 (m, 2H), 7.87 (m, 2H), 11.40 (br s, 1H)		Method 9

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### Example 80

#### (N,N-Dimethylsulphamoylmethyl)(4-chlorophenyl)ketone

To a stirred solution of methyl-4-chlorobenzoate (500mg, 2.94mmol) and *N,N*-dimethylmethanesulphonamide (302mg, 2.45mmol) in ethylene glycol dimethyl ether (15ml)

20 was added NaH (60% suspension in mineral oil, 265mg, 6.62mmol). The reaction was warmed to 85°C and stirred at this temperature for 3 hours. The reaction was cooled to room temperature and then quenched with water (~40ml). The water was extracted with ether then the ether was extracted with 1M NaOH. The aqueous fractions were combined and acidified to ~pH3 by the addition of concentrated HCl. The resulting suspension was extracted with

DCM (2 x 40ml), the DCM layers were combined, washed with water and brine then dried, filtered and evaporated to yield an oil. This oil was purified by column chromatography (20g Si, DCM to 1% MeOH/DCM) to yield a solid (325mg, 42%). NMR (DMSO-d<sub>6</sub>): 2.95 (s, 6H), 4.55 (s, 2H), 7.50 (d, 2H), 8.00 (d, 2H); m/z 262 [M+H]<sup>+</sup>.

5

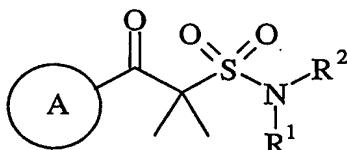
### Example 81

#### [2-(N,N-Diisopropylsulphamoyl)-2-(methyl)ethyl](4-fluorophenyl)ketone

Methyl iodide (51μl, 0.825mmol) was added to a stirred mixture of (N,N-diisopropylsulphamoylmethyl)(4-fluorophenyl)ketone (Example 3; 100mg, 0.33mmol) and 10 potassium carbonate (114mg, 0.825mmol) in DMF (5ml) at room temperature under an inert atmosphere. The reaction mixture was stirred overnight before quenching with water (50ml) and then extraction with EtOAc (2x50ml). The organics were washed with brine (50ml) and then dried over magnesium sulphate. The solvent was then removed under reduced pressure and the resulting brown gum was purified by chromatography (eluting with 10% 15 EtOAc/isohexane) to yield a colourless oil which solidified on scratching (57mgs, 53%). NMR (DMSO-d<sub>6</sub>): 1.22 (d, 12H), 1.62 (s, 6H), 3.61 (m, 2H), 7.28 (m, 2H), 8.02 (m, 2H).

### Examples 82-90

The procedure described in Example 81 was repeated using the appropriate starting 20 material(s) in place of (N,N-diisopropylsulphamoylmethyl)(4-fluorophenyl)ketone (Example 3) to give the following Examples.

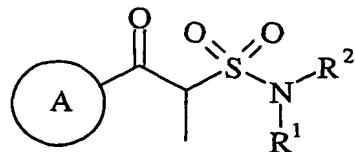


Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
82	2,4-Difluorophenyl	i-Pr	i-Pr	1.36 (d, 12H), 1.65 (s, 6H), 3.72 (m, 2H), 6.87 (m, 2H), 7.90 (m, 1H)		Example 31
83	3-Chlorophenyl	Me	Me		290	Example 4
84	4-Chloro-3-fluorophenyl	Me	Me		308	Example 20

Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	NMR	M/z	SM
85	4-Trifluoro-methylphenyl	Me	Me	1.64 (s, 6H), 2.91 (s, 6H), 7.83 (m, 2H), 7.93 (m, 2H)	324	Example 17
86	4-Cyanophenyl	i-Pr	i-Pr	1.33 (d, 12H), 1.71 (s, 6H), 3.64 (m, 2H), 7.72 (m, 2H), 8.12 (m, 2H)		Example 38
87	4-Fluorophenyl	Me	Pr		302	Example 9
88	4-Fluorophenyl	Me	-(CH <sub>2</sub> ) <sub>2</sub> -OMe		318	Example 8
89	2,4-Difluorophenyl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> -OMe	1.34 (d, 6H), 1.65 (s, 6H), 3.35 (s, 3H), 3.40 (m, 2H), 3.53 (m, 2H), 3.97 (m, 1H), 6.87 (m, 2H), 7.77 (m, 1H)	364	Example 61
90	4-Fluorophenyl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> -O-iPr		374	Example 55

### Examples 91-93

The procedure described in Example 81 was repeated using the appropriate starting material(s) in place of (*N,N*-diisopropylsulphamoylmethyl)(4-fluorophenyl)ketone (Example 5 3) to give the following Examples.



Ex	Ring A	R <sup>1</sup>	R <sup>2</sup>	M/z	SM
91	4-Fluorophenyl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> -O-iPr	358 (M-H) <sup>-</sup>	Example 55
92	2-Chlorothien-5-yl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> -OMe	352 (M-H) <sup>-</sup>	Example 60
93	Benzothien-2-yl	i-Pr	-(CH <sub>2</sub> ) <sub>2</sub> -O-iPr	396 (M-H) <sup>-</sup>	Example 54

**Example 94****[2-(*N,N*-Diisopropylsulphamoyl)ethyl][4-(*t*-butyldimethylsilyloxy)phenyl]ketone**

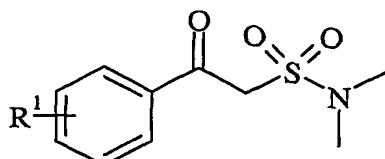
Methyl iodide (2.33ml, 37.5mmol) was added to a stirred mixture of (*N,N*-diisopropylsulphamoylmethyl)[4-(*t*-butyldimethylsilyloxy)phenyl]ketone (Example 62; 5 7.5mmol) and potassium carbonate (5.18g, 37.5mmol) in acetone (60ml) at room temperature under an inert atmosphere. The reaction mixture was stirred overnight at room temperature before adding more methyl iodide (2.33ml, 37.5mmol) and heating at reflux for 1 hour. The reaction mixture was quenched with water (200ml) and then extracted with EtOAc (2x150ml). The organics were dried over magnesium sulphate before being removed under reduced 10 pressure. The resulting orange oil was purified by chromatography (eluting with 10% EtOAc/isohexane) to yield a colourless oil (1.542g, 48%). NMR: 0.15 (s, 6H), 0.89 (s, 12H), 1.18 (m, 12H), 1.55 (d, 3H), 3.58 (m, 2H), 4.84 (q, 1H), 6.79 (d, 2H), 7.87 (d, 2H).

**Example 95****(*N,N*-Dimethylsulphamoylmethyl)(3-methylphenyl)ketone**

*N,N*-dimethylaminomethanesulphonamide (37mg, 0.3mmol) and anhydrous THF (3ml) were placed in a tube. To this solution was added a 1M solution of lithium bis(trimethylsilyl)amide in THF (0.6ml, 0.6mmol). The reaction was allowed to stir at room temperature for 30 minutes. At this point a solution of ethyl 3-methylbenzoate (60mg, 20 0.36mmol) in anhydrous THF (1ml) was added. The reaction was stirred at room temperature for 2 hours then quenched with sat ammonium chloride solution (2ml). The tube was capped then shaken and allowed to settle. The organic layer was collected and evaporated under reduced pressure, the resulting crude material was purified by prep LCMS (1-40% over 9.5mins, acetonitrile/water, with a constant 5ml/min 4% formic acid / acetonitrile) to yield a 25 solid (29mg, 40%). M/z: 242.

**Examples 96-106**

The procedure described in Example 95 was repeated using the appropriate ester in place of ethyl 3-methylbenzoate.



Ex	R <sup>1</sup>	NMR	MS
96	3-CH <sub>2</sub> =CHCH <sub>2</sub> -		268
97	4-CN		253
98	3-F	3.00 (s, 6H), 4.50 (s, 2H), 7.35 (m, 1H), 7.50 (m, 1H), 7.75 (m, 1H), 7.85 (d, 1H)	246
99	3-CN		253
100	4-MeC(O)-		268 (M-H) <sup>-</sup>
101	2-F		246
102	2,4-diF	2.95 (s, 6H), 4.60 (s, 2H), 6.90 (m, 1H), 7.00 (m, 1H), 7.95 (m, 1H)	262 (M-H) <sup>-</sup>
103	3-MeO, 4-Cl		290 (M-H) <sup>-</sup>
104	4-HC≡C-		252
105	4-CH <sub>2</sub> =CH-CH <sub>2</sub> -O-		284
106	3,4,5-triMeO-	NMR (DMSO-d <sub>6</sub> ): 2.80 (s, 6H), 3.80 (s, 3H), 3.85 (s, 6H), 4.95 (s, 2H), 7.35 (s, 2H)	318

**Example 107****(4-Fluorophenyl)-[1-(N,N-diisopropylsulphamoyl)cyclopentyl]ketone**

1,4-Dibromobutane (373 mgs, 1.7 mmol) was added drop wise to a stirred mixture of 5 (N,N-diisopropylsulphamoylmethyl)(4-fluorophenyl)ketone (Example 3; 400 mgs, 1.33 mmol) and potassium carbonate (460 mgs, 3.3 mmol) in dimethylformamide (5ml). After stirring overnight the reaction mixture was quenched with water and extracted with EtOAc. The EtOAc phase was washed with water, brine and dried (MgSO<sub>4</sub>). Removal of the EtOAc gave a brown oil which was chromatographed (9g silica cartridge, eluent 10% EtOAc in 10 Hexane) to give the required product (80 mgs). NMR (DMSO-d<sub>6</sub>) 1.15-1.37 (d, 12H), 1.37-1.59 (m, 2H), 1.65-1.92 (m, 2H), 2.49-2.74 (m, 4H), 3.50-3.65 (m, 2H), 7.02-7.19 (m, 2H), 8.17-8.32 (m, 2H). m/z: 340.14 (M-CH<sub>3</sub>)..

**Preparation of Starting Materials**

15 The starting materials for the Examples above are either commercially available or are readily prepared by standard methods from known materials. For example the following reactions are illustrations but not limitations of the preparation of some of the starting materials used in the above reactions.

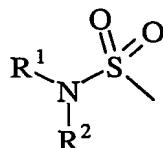
**Method 1****1-Methoxy-2-[N-(methyl)mesylaminoethyl]**

To a stirred solution of N-(2-methoxyethyl)methylamine (750mg, 8.43mmol) and triethylamine (938mg, 9.27mmol) in anhydrous DCM (60ml) at 0°C was added mesylchloride 5 (966mg, 8.43mmol). The reaction was stirred at 0°C for 10 minutes then allowed to warm to room temperature and left to stir for a further 30 minutes. The reaction was then transferred to a separating funnel and washed with 2M HCl (20ml), water (20ml) and brine (20ml) then dried, filtered and evaporated to yield the product as a pale yellow oil (935mg, 67%). NMR: 2.85 (s, 3H), 2.95 (s, 3H), 3.40 (m, 5H), 3.55 (t, 2H).

10

**Methods 2-3**

The procedure described in Method 1 was repeated using the appropriate amine in place of N-(2-methoxyethyl)methylamine.



Meth	R <sup>1</sup>	R <sup>2</sup>	NMR
2	Me	Pr	0.95 (t, 3H), 1.60 (m, 2H), 2.80 (s, 3H), 2.95 (s, 3H), 3.10 (t, 2H)
3	Et	i-Pr	1.25 (m, 9H), 2.85 (s, 3H), 3.20 (q, 2H), 4.10 (m, 1H)
4	H	-(CH <sub>2</sub> ) <sub>2</sub> -OCH <sub>3</sub>	2.99 (s, 3H), 3.31(m, 2H), 3.40 (s, 3H), 3.53 (m, 2H), 4.92 (br s, 1H)
5	H	-(CH <sub>2</sub> ) <sub>2</sub> -O-iPr	1.17 (d, 6H), 2.99 (s, 3H), 3.28 (m, 2H), 3.55 (t, 2H), 3.62 (m, 1H), 4.82 (br s, 1H)

15

**Method 6****1-(N,N-Dimethylamino)-2-[N-(methyl)mesylaminoethyl]**

To a stirred solution of *N,N,N*-trimethylethylenediamine (1.02g, 10mmol) and triethylamine (1.11g, 11mmol) in anhydrous DCM (70ml) at 0°C was added mesylchloride 20 (1.15g, 10mmol). The reaction was stirred at 0°C for 10 minutes then allowed to warm to room temperature and left to stir for a further 30 minutes. Volatiles removed under reduced pressure and resulting oil taken up in DCM (60ml) then washed with 2M NaOH (30ml) and

brine (30ml). The solvent was removed under reduced pressure to yield the product as an oil (962mg, 53%). NMR: 2.30 (s, 6H), 2.50 (t, 2H), 2.85 (s, 3H), 2.90 (s, 3H), 3.30 (t, 2H).

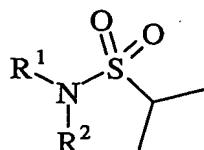
### Method 7

5 Propane-2-sulphonic acid dimethyl amide

To a stirred solution of 2M dimethylamine in THF (5.35ml, 10.7mmol) and pyridine (865 $\mu$ l, 10.7mmol) in anhydrous THF (10ml) was added isopropylsulphonylchloride (1ml, 8.9mmol). The reaction was stirred at room temperature overnight. Volatiles removed under reduced pressure and resulting oil taken up in EtOAc (60ml) then washed with 0.5M HCl 10 (30ml) and water (30ml). The solvent was dried over magnesium sulphate and then removed under reduced pressure to yield the product as an orange oil (688mg, 51%). NMR: 1.36 (d, 6H), 2.93 (s, 6H), 3.25 (m, 1H).

### Methods 8-9

15 The procedure described in Method 7 was repeated using the appropriate amine in place of dimethylamine.



Meth	R¹	R²	NMR
8	Me	i-Pr	(DMSO-d <sub>6</sub> ) 1.10 (d, 6H), 1.18 (d, 6H), 2.68 (s, 3H), 3.24 (m, 1H), 3.94 (m, 1H)
9	H	i-Pr	(DMSO-d <sub>6</sub> ) 1.05 (d, 6H), 1.10 (d, 6H), 3.06 (m, 1H), 3.40 (m, 1H), 6.80 (d, 1H)

### Method 10

20 N-Isopropyl-N-(2-methoxy-ethyl)-methanesulphonamide

To a stirred solution of *N*-(2-methoxy-ethyl)-methanesulphonamide (Method 4) (1.2g, 7.7mmol) in DMF (20ml) under an inert atmosphere was added sodium hydride (400mg, 10mmol). 2-Bromopropane (1.73ml, 18.48mmol) was added and the reaction heated at 70°C for 7h. The reaction mixture was quenched with water (100ml) and then extracted into EtOAc 25 (100ml). The organics were further washed with brine (100ml) before being dried over magnesium sulphate. The solvent was then removed under reduced pressure to yield the

product as a yellow oil (600mg, 40%). NMR: 1.26 (d, 6H), 2.88 (s, 3H), 3.31 (m, 2H), 3.38 (s, 3H), 3.55 (m, 2H), 4.09 (m, 1H).

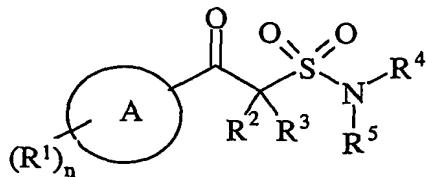
### Method 11

#### 5 *N*-Isopropyl-*N*-(2-isopropoxy-ethyl)-methanesulphonamide

The procedure described in Method 10 was repeated using *N*-(2-isopropoxyethyl)methanesulphonamide (Method 5) in place of *N*-(2-methoxy-ethyl)-methanesulphonamide. NMR: 1.16 (d, 6H), 1.27 (d, 6H), 2.90 (s, 3H), 3.29 (m, 2H), 3.56 (m, 3H), 4.09 (m, 1H).

Claims

1. The use of a compound of formula (I):



5

(I)

wherein:

**Ring A** is selected from carbocyclyl or heterocyclyl;

**R¹** is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy,

10 *N*-(C<sub>1-4</sub>alkyl)amino, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, C<sub>1-4</sub>alkanoylamino, *N*-(C<sub>1-4</sub>alkyl)carbamoyl, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, *N*-(C<sub>1-4</sub>alkyl)sulphamoyl, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino, tri-(C<sub>1-4</sub>alkyl)silyloxy, carbocyclyl, heterocyclyl, carbocyclylC<sub>0-4</sub>alkylene-Y- and heterocyclylC<sub>0-4</sub>alkylene-Y-; wherein R<sup>1</sup> may be optionally substituted on carbon by one or

15 more groups selected from R<sup>6</sup>; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R<sup>7</sup>;

n is 0-5; wherein the values of R<sup>1</sup> may be the same or different;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen, hydroxy, amino, cyano,

16 C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, *N*-(C<sub>1-4</sub>alkyl)amino, *N,N*-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, carbocyclyl, heterocyclyl, carbocyclylC<sub>1-4</sub>alkyl, heterocyclylC<sub>1-4</sub>alkyl; or R<sup>2</sup> and R<sup>3</sup> together form C<sub>2-6</sub>alkylene; wherein R<sup>2</sup> and R<sup>3</sup> may be independently optionally substituted on carbon by one or more groups selected from R<sup>8</sup>; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R<sup>9</sup>;

one of R<sup>4</sup> and R<sup>5</sup> is selected from C<sub>1-4</sub>alkyl and the other is selected from hydrogen or

25 C<sub>1-4</sub>alkyl; wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>;

Y is -S(O)<sub>a</sub>- , -O-, -NR<sup>12</sup>- , -C(O), -C(O)NR<sup>13</sup>- , -NR<sup>14</sup>C(O)- or -SO<sub>2</sub>NR<sup>15</sup>- ; wherein a is

0 to 2;

R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup> and R<sup>15</sup> are independently selected from hydrogen, phenyl and C<sub>1-4</sub>alkyl;

30 R<sup>6</sup> and R<sup>8</sup> are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C<sub>1-4</sub>alkyl,

C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, N-(C<sub>1-4</sub>alkyl)amino, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, C<sub>1-4</sub>alkanoylamino, N-(C<sub>1-4</sub>alkyl)carbamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, N-(C<sub>1-4</sub>alkyl)sulphamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino, carbocyclyl 5 and heterocyclyl; wherein R<sup>6</sup> and R<sup>8</sup> may be independently optionally substituted on carbon by one or more R<sup>11</sup>;

R<sup>10</sup> is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, N-(C<sub>1-4</sub>alkyl)amino, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, 10 C<sub>1-4</sub>alkanoylamino, N-(C<sub>1-4</sub>alkyl)carbamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, N-(C<sub>1-4</sub>alkyl)sulphamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino; wherein R<sup>10</sup> may be independently optionally substituted on carbon by one or more R<sup>16</sup>;

R<sup>7</sup> and R<sup>9</sup> are independently selected from C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkylsulphonyl, 15 C<sub>1-4</sub>alkoxycarbonyl, carbamoyl, N-(C<sub>1-4</sub>alkyl)carbamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R<sup>11</sup> and R<sup>16</sup> are independently selected from halo, nitro, cyano, hydroxy, trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, 20 diethylamino, N-methyl-N-ethylamino, acetylarnino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio, ethylthio, methylsulphanyl, ethylsulphanyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N-methylsulphamoyl, N-ethylsulphamoyl, N,N-dimethylsulphamoyl, N,N-diethylsulphamoyl or N-methyl-N-ethylsulphamoyl;

25 or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11 $\beta$ HSD1.

2. The use according to claim 1 wherein Ring A is pyridyl, phenyl, thienyl, furyl, pyrazinyl, 1,2,3-thiadiazolyl, thiazolyl, cyclohexyl, naphthyl, cyclohexenyl, pyrazolyl, 30 benzothienyl, indolyl, 1,1,3-trioxo-2,3-dihydro-1,2-benzisothiazolyl, 1,3-benzodioxolyl, cyclopentyl, tetrahydropyranyl, 1-oxooctahydropyrido[1,2-a]pyrazinyl, 1,2,3,4-tetrahydronaphthyl, piperidinyl and benzthiazolyl.

3. The use according to either of claims 1 or 2 wherein R<sup>1</sup> is selected from halo, nitro, cyano, sulphamoyl, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, tri-(C<sub>1-4</sub>alkyl)silyloxy, carbocyclyl and heterocyclylC<sub>0-4</sub>alkylene-Y-; wherein R<sup>1</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>; wherein

5 Y is -NR<sup>12</sup>-;

R<sup>12</sup> is hydrogen; and

R<sup>6</sup> is selected from halo, C<sub>2-4</sub>alkenyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoylamino and carbocyclyl.

10 4. The use according to any one of claims 1-4 wherein n is 0-2; wherein the values of R<sup>1</sup> may be the same or different.

5. The use according to any one of claims 1-5 wherein R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen or C<sub>1-4</sub>alkyl, or R<sup>2</sup> and R<sup>3</sup> together form C<sub>2-6</sub>alkylene.

15

6. The use according to any one of claims 1-6 wherein one of R<sup>4</sup> and R<sup>5</sup> is selected from hydrogen and C<sub>1-4</sub>alkyl and the other is selected from C<sub>1-4</sub>alkyl; wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>; and

R<sup>10</sup> is selected from C<sub>1-4</sub>alkoxy and N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino.

20

7. The of a compound of formula (I) (as depicted in claim 1) wherein:

Ring A is carbocyclyl or heterocyclyl;

R<sup>1</sup> is selected from halo, nitro, cyano, sulphamoyl, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, tri-(C<sub>1-4</sub>alkyl)silyloxy, carbocyclyl and heterocyclylC<sub>0-4</sub>alkylene-Y-; 25 wherein R<sup>1</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>; wherein:

Y is -NR<sup>12</sup>-;

R<sup>12</sup> is hydrogen; and

R<sup>6</sup> is selected from halo, C<sub>2-4</sub>alkenyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoylamino and

30 carbocyclyl;

n is 0-3; wherein the values of R<sup>1</sup> may be the same or different;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen or C<sub>1-4</sub>alkyl, or R<sup>2</sup> and R<sup>3</sup> together form C<sub>2-6</sub>alkylene;

one of R<sup>4</sup> and R<sup>5</sup> is selected from hydrogen and C<sub>1-4</sub>alkyl and the other is selected from C<sub>1-4</sub>alkyl; wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>; and

R<sup>10</sup> is selected from C<sub>1-4</sub>alkoxy and N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino;

5 or a pharmaceutically acceptable salt thereof;

in the manufacture of a medicament for use in the inhibition of 11 $\beta$ HSD1.

8. A compound of formula (I) as depicted in claim 1 selected from:

(4-fluorophenyl)[N-(2-methoxyethyl)-N-(methyl)sulphamoylmethyl]ketone;

10 (2,4-difluorophenyl)[1-(N,N-diisopropylsulphamoyl)-1methylethyl]ketone;

(2,4-difluorophenyl)(N,N-diisopropylsulphamoylmethyl)ketone;

(thiazol-2-yl)(N,N-dimethylsulphamoylmethyl)ketone;

(4-fluorophenyl)[N-(2-isopropoxyethyl)-N-(isopropyl)sulphamoylmethyl]ketone;

(pyrazin-2-yl)(N,N-dimethylsulphamoylmethyl)ketone;

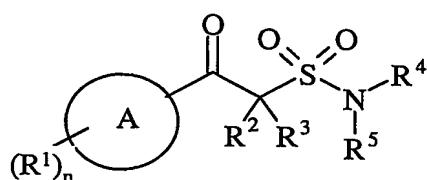
15 (4-isopropoxyphenyl)(N,N-diisopropylsulphamoylmethyl)ketone;

(3-cyanophenyl)(N,N-diisopropylsulphamoylmethyl)ketone;

(pyrid-2-yl)(N,N-dimethylsulphamoylmethyl)ketone;

or a pharmaceutically acceptable salt thereof.

20 9. A compound of formula (Ia):



wherein:

**Ring A** is selected from phenyl, pyridyl, thiazolyl, thienyl and furyl;

25 R<sup>1</sup> is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto,

sulphamoyl, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy,

N-(C<sub>1-4</sub>alkyl)amino, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, C<sub>1-4</sub>alkanoylamino, N-(C<sub>1-4</sub>alkyl)carbamoyl,

N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl,

N-(C<sub>1-4</sub>alkyl)sulphamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino; wherein R<sup>1</sup>

30 may be optionally substituted on carbon by one or more groups selected from R<sup>6</sup>; and wherein

if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R<sup>7</sup>;

n is 0-3; wherein the values of R<sup>1</sup> may be the same or different;

R<sup>2</sup> and R<sup>3</sup> are independently selected from hydrogen, hydroxy, amino, cyano,

5 C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkoxy, N-(C<sub>1-4</sub>alkyl)amino, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, carbocyclyl, heterocyclyl, carbocyclylC<sub>1-4</sub>alkyl, heterocyclylC<sub>1-4</sub>alkyl; wherein R<sup>2</sup> and R<sup>3</sup> may be independently optionally substituted on carbon by one or more groups selected from R<sup>8</sup>; and wherein if said heterocyclyl contains an -NH- moiety that nitrogen may be optionally substituted by a group selected from R<sup>9</sup>;

10 R<sup>4</sup> and R<sup>5</sup> are independently selected from C<sub>1-4</sub>alkyl; wherein R<sup>4</sup> and R<sup>5</sup> may be optionally substituted on carbon by one or more groups selected from R<sup>10</sup>;

R<sup>6</sup> and R<sup>8</sup> are independently selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl, mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, N-(C<sub>1-4</sub>alkyl)amino, 15 N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, C<sub>1-4</sub>alkanoylamino, N-(C<sub>1-4</sub>alkyl)carbamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, N-(C<sub>1-4</sub>alkyl)sulphamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino; wherein R<sup>6</sup> and R<sup>8</sup> may be independently optionally substituted on carbon by one or more R<sup>11</sup>;

R<sup>10</sup> is selected from halo, nitro, cyano, hydroxy, amino, carboxy, carbamoyl,

20 mercapto, sulphamoyl, trifluoromethyl, trifluoromethoxy, C<sub>1-4</sub>alkyl, C<sub>2-4</sub>alkenyl, C<sub>2-4</sub>alkynyl, C<sub>1-4</sub>alkoxy, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkanoyloxy, N-(C<sub>1-4</sub>alkyl)amino, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>amino, C<sub>1-4</sub>alkanoylamino, N-(C<sub>1-4</sub>alkyl)carbamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, C<sub>1-4</sub>alkylS(O)<sub>a</sub> wherein a is 0 to 2, C<sub>1-4</sub>alkoxycarbonyl, N-(C<sub>1-4</sub>alkyl)sulphamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>sulphamoyl, C<sub>1-4</sub>alkylsulphonylamino; wherein R<sup>10</sup> may be independently 25 optionally substituted on carbon by one or more R<sup>16</sup>;

R<sup>7</sup> and R<sup>9</sup> are independently selected from C<sub>1-4</sub>alkyl, C<sub>1-4</sub>alkanoyl, C<sub>1-4</sub>alkylsulphonyl, C<sub>1-4</sub>alkoxycarbonyl, carbamoyl, N-(C<sub>1-4</sub>alkyl)carbamoyl, N,N-(C<sub>1-4</sub>alkyl)<sub>2</sub>carbamoyl, benzyl, benzyloxycarbonyl, benzoyl and phenylsulphonyl;

R<sup>11</sup> and R<sup>16</sup> are independently selected from halo, nitro, cyano, hydroxy,

30 trifluoromethoxy, trifluoromethyl, amino, carboxy, carbamoyl, mercapto, sulphamoyl, methyl, ethyl, methoxy, ethoxy, acetyl, acetoxy, methylamino, ethylamino, dimethylamino, diethylamino, N-methyl-N-ethylamino, acetylarnino, N-methylcarbamoyl, N-ethylcarbamoyl, N,N-dimethylcarbamoyl, N,N-diethylcarbamoyl, N-methyl-N-ethylcarbamoyl, methylthio,

ethylthio, methylsulphanyl, ethylsulphanyl, mesyl, ethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, *N*-methylsulphamoyl, *N*-ethylsulphamoyl, *N,N*-dimethylsulphamoyl, *N,N*-diethylsulphamoyl or *N*-methyl-*N*-ethylsulphamoyl; or a pharmaceutically acceptable salt thereof; with the proviso that said compound is not (*N*-methyl-*N*-butylsulphamoylmethyl)(phenyl)ketone; [1-(*N,N*-dimethylsulphamoyl)ethyl](phenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(4-nitrophenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(4-fluoro-2-methylaminophenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(3-methoxy-4-methyl-6-aminophenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(3-methoxy-6-aminophenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(phenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(2-nitro-4-methoxyphenyl)ketone; (*N,N*-dimethylsulphamoylmethyl)(2-amino-4-methoxyphenyl)ketone; [1-(*N*-methyl-*N*-butylsulphamoyl)ethyl](phenyl)ketone; or (*N,N*-dimethylsulphamoylmethyl)(thien-2-yl)ketone.

15 10. A pharmaceutical composition which comprises a compound of formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, as claimed in either of claims 8 or 9 in association with a pharmaceutically-acceptable diluent or carrier.

11. A compound of the formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, 20 as claimed in either of claims 8 or 9, for use in a method of prophylactic or therapeutic treatment of a warm-blooded animal, such as man.

12. A compound of the formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, as claimed in either of claims 8 or 9, for use as a medicament.

25 13. The use of a compound of the formula (I) or (Ia), or a pharmaceutically acceptable salt thereof, as claimed in either of claims 8 or 9, in the manufacture of a medicament for use in the production of an 11 $\beta$ HSD1 inhibitory effect in a warm-blooded animal, such as man.

30 14. The use of a compound as claimed in any one of claims 1-7 or 13 wherein production of, or producing an, 11 $\beta$ HSD1 inhibitory effect refers to the treatment of metabolic syndrome.

15. The use of a compound as claimed in any one of claims 1-7 or 13 wherein production of, or producing an, 11 $\beta$ HSD1 inhibitory effect refers to the treatment of diabetes, obesity, hyperlipidaemia, hyperglycaemia, hyperinsulinemia or hypertension, particularly diabetes and obesity.

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16. The use of a compound as claimed in any one of claims 1-7 or 13 wherein production of, or producing an, 11 $\beta$ HSD1 inhibitory effect refers to the treatment of glaucoma, osteoporosis, tuberculosis, dementia, cognitive disorders or depression.

10 17. A method for producing an 11 $\beta$ HSD1 inhibitory effect in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula (I), as claimed in any one of claims 1-8, or a compound of formula (Ia) as claimed in claim 9, or a pharmaceutically acceptable salt thereof.

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## INTERNATIONAL SEARCH REPORT

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	A61K31/18	A61K31/33	C07C311/13	C07D213/50	C07C311/27
	C07D277/46	C07D241/12	C07D317/56	C07D277/32	C07D333/56
	C07D333/28	A61P3/00			

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	P. GAYRAL ET AL: ARZNEIM.-FORSCH.-DRUG RES., vol. 45, no. 10, 1995, pages 1122-1127, XP0001153451 page 1124, column 1, 2-oxo-2-arylethanesulfonamides: compound 5x	9
X	EP 0 206 616 A (BOOTS CO PLC) 30 December 1986 (1986-12-30) example 17 a	9
A	examples 14a, 15e, 21a; claim 29	9
A	DATABASE CASREACT AMERICAN CHEMICAL SOCIETY; XP002270882 retrieved from STN Database accession no. 72:89988 abstract; RN 408508-55-4	9
	-/-	

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

20 February 2004

Date of mailing of the international search report

09/03/2004

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## INTERNATIONAL SEARCH REPORT

PCT/GB 03/04766

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	& J.B. HENDRICKSON ET AL: TETRAHEDRON LETT., no. 5, 1970, pages 343-348, -----	
A	J.A. VEGA ET AL: TETRAHEDRON, vol. 54, no. 14, 1998, pages 3589-3606, XP0004110504 page 3593, table 2, entries 5-6 -----	9
A	M. LECLERCQ ET AL: TETRAHEDRON LETT., vol. 31, no. 27, 1990, pages 3875-3878, XP002270880 page 3876, line 5 -----	9
A	DATABASE CAPLUS AMERICAN CHEMICAL SOCIETY; XP002270883 retrieved from STN Database accession no. 1978:509326 abstract; RN 67323-27-7 & R. ALBRECHT: JUSTUS LIEBIGS ANNALEN DER CHEMIE, no. 4, 1978, pages 617-626, -----	9
A	DATABASE CAPLUS AMERICAN CHEMICAL SOCIETY; XP002270884 retrieved from STN Database accession no. 1976:16883 abstract; RN 58044-88-5 & J.B. HENDRICKSON ET AL: TETRAHEDRON, vol. 31, no. 20, 1975, pages 2517-2521, -----	9
A	G.M. COPPOLA ET AL: J. HETEROCYCL. CHEM., vol. 16, 1979, pages 1605-1610, XP002270881 page 1610, compound 93 -----	9
A	WO 01/90090 A (BIOVITRUM AB) 29 November 2001 (2001-11-29) claims 6-12 -----	1,14-17

## INTERNATIONAL SEARCH REPORT

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### Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
Although claim 17 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

#### Remark on Protest

The additional search fees were accompanied by the applicant's protest.  
 No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

PCT/GB 03/04766

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
EP 0206616	A	30-12-1986		AU 5838286 A DD 249010 A5 DK 272386 A EP 0206616 A2 ES 8801211 A1 FI 862519 A GR 861528 A1 HU 42073 A2 JP 62036361 A NO 862372 A PH 22992 A PT 82760 A ,B US 4772614 A ZA 8604288 A		18-12-1986 26-08-1987 16-12-1986 30-12-1986 01-03-1988 16-12-1986 10-10-1986 29-06-1987 17-02-1987 16-12-1986 24-02-1989 01-07-1986 20-09-1988 28-01-1987
WO 0190090	A	29-11-2001		AU 6093101 A AU 6093201 A AU 6283001 A AU 6283101 A AU 6445601 A BR 0111099 A CA 2408142 A1 CA 2408144 A1 CA 2408783 A1 CA 2409697 A1 CN 1430615 T CN 1430614 T CN 1437588 T CN 1438997 T DE 1283831 T1 EP 1283831 A1 EP 1283832 A1 EP 1283834 A1 EP 1283833 A1 HU 0302435 A2 JP 2003534336 T JP 2003534337 T JP 2003534338 T JP 2003534339 T NO 20025585 A NO 20025586 A NO 20025587 A NO 20025588 A WO 0190093 A1 WO 0190090 A1 WO 0190091 A1 WO 0190094 A1 WO 0190092 A1 US 2003176476 A1 US 2003199501 A1 US 2003166689 A1		03-12-2001 03-12-2001 03-12-2001 03-12-2001 03-12-2001 15-04-2003 29-11-2001 29-11-2001 29-11-2001 29-11-2001 16-07-2003 16-07-2003 20-08-2003 27-08-2003 14-08-2003 19-02-2003 19-02-2003 19-02-2003 19-02-2003 29-12-2003 18-11-2003 18-11-2003 18-11-2003 18-11-2003 23-12-2002 21-01-2003 21-01-2003 20-12-2002 29-11-2001 29-11-2001 29-11-2001 29-11-2001 18-09-2003 23-10-2003 04-09-2003